BMJ Paediatrics Open

Preterm children's developmental coordination disorder, cognition and quality of life

Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2019-000633
Article Type:	Original research
Date Submitted by the Author:	08-Jan-2020
Complete List of Authors:	Uusitalo, Karoliina; University of Turku, Pediatric Neurology; Turku University Hospital Haataja, Leena; University of Helsinki, Pediatric Neurology; Helsinki University Hospital, Children's Hospital, Pediatric Research Center Nyman, Anna; University of Turku, Psychology Ripatti, Liisi; Turku University Hospital, Pediatric Surgery Huhtala, Mira; Turku University Hospital, Oncology and Radiotherapy Rautava, Päivi; University of Turku, Public Health; Clinical Research Center Lehtonen, Prof Liisa; University of Turku, Pediatrics; Turku University Hospital, Pediatrics Parkkola, Riitta; University of Turku, Radiology; Turku PET Centre Lahti, Katri; University of Turku, Pediatric neurology; Turku University Hospital Koivisto, Mari; University of Turku Setänen, Sirkku; Uppsala Universitet, Women's and Children's Health; University of Turku, Pediatric Neurology
Keywords:	Neurodevelopment, Outcomes research, Neonatology

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Preterm children's developmental coordination disorder, cognition and quality of life

Karoliina Uusitalo[a,b], MD, Leena Haataja[c], MD, PhD, Anna Nyman[d], PhD, Liisi Ripatti[e], MD, PhD, Mira Huhtala[f], MD, PhD, Päivi Rautava[g,h], MD, PhD, Liisa Lehtonen[b,i], MD, PhD, Riitta Parkkola[b,j], MD, PhD, Katri Lahti[a,b], MD, Mari Koivisto[h], MSc, Sirkku Setänen[a,b,k], MD, PhD, on behalf of the PIPARI Study Group

Affiliations: [a]Department of Pediatric Neurology, University of Turku, Turku, Finland; [b]Turku University Hospital, Turku, Finland; [c]Department of Pediatric Neurology, Children's Hospital, Pediatric Research Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [d]Department of Psychology, University of Turku, Turku, Finland; [e]Department of Pediatric Surgery, Turku University Hospital, Turku, Finland, [f]Department of Oncology and Radiotherapy, Turku University Hospital, Turku, Finland, [g]Department of Public Health, University of Turku, Turku, Finland; [h]Clinical Research Centre, Turku, Finland, [i]Department of Pediatrics, University of Turku, Turku, Finland; [j]Department of Radiology, and Turku PET Center, University of Turku; [k]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

Address correspondence to: Sirkku Setänen, Department of Women's and Children's Health, Uppsala University, Akademiska sjukhuset, 751 85 Uppsala, Uppsala, Sweden. Email: sirkku.setanen@kbh.uu.se

Word count: 2634

Abbreviations:
CP – cerebral palsy
DCD – developmental coordination disorder
IQ – intelligence quotient
HRQoL – health-related quality of life
Movement ABC-2 – Movement Assessment Battery for Children – Second Edition
WISC-IV – Wechsler Intelligence Scale for Children – Fourth Edition
17D – 17-dimensional illustrated questionnaire

What is known about this topic:

- The incidence of cerebral palsy has decreased in children born very preterm.
- Children born very preterm still have an increased risk for developmental coordination disorder (DCD).
- DCD may co-occur with cognitive dysfunction and lower health-related quality of life (HRQoL).

What this study adds:

- Very preterm born children with DCD had adverse cognitive development and self-experienced HRQoL compared with preterm children without motor impairment.
- This group of very preterm born children reported better HRQoL in comparison with Finnish norms.

Contributors' Statement Page

Dr Uusitalo collected the data, drafted the initial manuscript, and revised the manuscript.

Prof Haataja and Prof Lehtonen conceptualized and designed the study, designed the data collection instrument, supervised the data collection, revised the manuscript, and critically reviewed the study for its intellectual content.

PhD Nyman collected data, revised the manuscript and reviewed the manuscript for its intellectual content.

Dr Huhtala, Dr Ripatti and Prof Rautava revised the manuscript, and critically reviewed the study for its intellectual content, ensured that accuracy of any part of the work are appropriately investigated and resolved, and moreover, they were the specialists on HRQoL-testing.

Prof Parkkola supervised the data collection, revised the manuscript, and critically reviewed the study for its intellectual content.

Dr Lahti collected data, and revised the manuscript and reviewed the manuscript for its intellectual content.

Mrs Koivisto performed the statistical analysis of the data, and revised and reviewed the manuscript for its intellectual content.

Dr Setänen designed the study, collected data, revised the manuscript, and critically reviewed the study for its intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Objective: To evaluate the rate of developmental coordination disorder (DCD), its correlation to cognition and self-experienced health-related quality of life (HRQoL) in children born very preterm.

Design: Prospective follow-up study.

Setting: Regional population of very preterm children born in Turku University Hospital, Finland, in 2001-2006.

Patients: A total of 170 very preterm children were followed up until 11 years of age.

Main outcome measures: Motor and cognitive outcomes were evaluated using the Movement Assessment Battery for Children - Second Edition (Movement ABC-2) and the Wechsler Intelligence Scale for Children - Fourth Edition, respectively, and HRQoL using a 17-dimensional illustrated questionnaire (17D). The Touwen neurological examination was performed to exclude other neurological conditions affecting the motor outcome.

Results: Eighteen children (17 boys) (11.3%) had DCD, defined as the Movement ABC-2 total test score $\leq 5^{th}$ percentile. A positive correlation between motor and cognitive outcome ($r=0.22$, $p=0.006$) was found. Children with DCD had lower cognitive scores than those without DCD (full-scale intelligence quotient mean 76.8 vs. 91.6, $p=0.001$). Moreover, children with DCD reported lower HRQoL than children without motor impairment (17D mean 0.93 vs. 0.96, $p=0.03$). However, the HRQoL was higher in this group of very preterm children compared to population based normative test results ($p<0.001$).

Conclusions: DCD was more common in very preterm children at 11 years of age than in the general population. DCD associated with adverse cognitive development and self-experienced HRQoL. However, this group of very preterm children reported better HRQoL in comparison with Finnish norms.

INTRODUCTION

The incidence of cerebral palsy (CP) has decreased among children born very preterm[1–6]. However, the rate of non-CP motor impairments such as developmental coordination disorder (DCD) has not decreased[7], and children born preterm are still at increased risk for cognitive impairment compared to term peers[8–11].

DCD is defined as motor problems interfering with academic achieving or activities of daily living which cannot be explained by medical, neurological or cognitive impairment[12]. The etiology of DCD is largely unknown, although it is proposed to result from abnormalities in the brain development and functioning[13]. The prevalence of DCD has been shown to vary from 5 to 6% in school-aged children and from 8 to 51% in those born preterm[8,12,14–16]. DCD has been shown to co-occur with developmental disorders such as social, behavioral and attention problems, and learning difficulties[12,14,17–19]. Nevertheless, data of the relationship between DCD and cognitive development in early adolescence is limited[19].

Severe neurodevelopmental impairments such as CP, cognitive impairment, hearing and visual impairment have been reported to associate with poorer self-experienced health-related quality of life (HRQoL) in school aged children born preterm, while those without these morbidities have reported HRQoL equal to peers[20,21]. The effect of preterm birth on HRQoL seems to be most significant in younger years and seems to decrease over time[22]. The impact of motor impairments such as DCD to HRQoL is not well known, and the reports have been controversial[23,24].

The aims of this study were to study the correlation between motor and cognitive development at 11 years of age; and to study the effect of DCD on self-experienced HRQoL. We hypothesized that poorer motor outcome correlates with adverse cognitive performance, and that DCD correlates with

lower perceived HRQoL as compared to children without motor impairment.

METHODS

Participants

This prospective study is part of the PIPARI (The Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age) study of very preterm infants. The participants were born to Finnish- or Swedish-speaking families from January 2001 to December 2006 in Turku University Hospital, Finland. From 2001 to 2003 the inclusion criteria were birth weight ≤1500g and prematurity (<37 gestational weeks). From 2004, the inclusion criteria were broadened to all infants born ≤32 weeks of gestational age irrespective of the birth weight. The exclusion criteria were severe congenital anomalies or diagnosed syndrome affecting cognitive development. The flow chart of the participants is shown in Figure 1. The Ethics Review Committee of the Hospital District of South-West Finland approved the study protocol in 2000 and in 2012. Written informed consent for this follow-up study were provided by parents and children. This study was done without patient and public involvement.

Motor outcome

The diagnosis of CP was confirmed based on the classification proposed by Himmelmann et al.[25] after a systematic clinical follow-up by two years of corrected age by an experienced child neurologist. The motor outcome of the children without CP was evaluated at 11 years of age by one of the three physicians by using Movement Assessment Battery for Children – Second Edition (Movement ABC-2)[26,27]. The raw scores were converted into total standard scores and percentile scores according to the test manual, using the age band 3 (11 to 16 years) and the norms for 11-year-old children. A total test score >15th percentile indicated no movement difficulty, >5th to 15th percentile indicated risk of movement difficulties, and ≤5th percentile denoted DCD[27]. Touwen neurological examination was systematically used to confirm that there were no other neurological conditions such as muscle diseases affecting the motor development[27–29]. The Movement ABC-2

examinations were video recorded in order to enable reassessment and to guarantee the comparability between examinations and no discrepancies were found.

Cognitive outcome

The cognitive development at 11 years of age was assessed with the Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV), Finnish translation[30,31]. The assessments were performed either in Finnish or Swedish according to child's native language. Finnish assessments were performed by one of the two psychologists and Swedish speaking children were assessed by a native Swedish-speaking psychologist. General intelligence was measured with full-scale intelligence quotient (IQ), which consisted of the Verbal Comprehension Index, the Perceptual Reasoning Index, the Working Memory Index and the Processing Speed Index. The classification was based on the test manual[30,31]. The scores were classified as average if the full-scale IQ was ≥90, low average 80-89, and borderline 70-79. A full-scale IQ <70 was classified as severe cognitive impairment.

Health-related quality of life

The self-experienced HRQoL at 11 years of age was evaluated using a generic self-assessment measure, a17-dimensional illustrated questionnaire (17D)[32]. It consisted of 17 multiple-choice questions of health and function. The domains were mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, school and hobbies, learning and memory, discomfort and symptoms, depression, distress, vitality, appearance, friends and concentration. Every domain had a five-level tick box functioning scale alternating from a perfect level to a severe dysfunction. The children completed the questionnaire by themselves or as an interview by the physician before the motor assessment. The relative weights of each dimension were defined in the instrument's home page[33]. The overall HRQoL was calculated from the health state descriptive system using population-based

preference or utility weights for 11-year-old healthy Finnish school children. The HRQoL score varied from zero (worst score, equals to death) to one (best score, equals complete health)[32].

Statistical Analysis

Difference in continuous background characteristics between study children and the drop-outs were studied using a two-sample t-test or a Wilcoxon two-sample test. For the categorical background characteristics, a chi-square test or Fisher's exact test were used. Correlations between the percentiles for the total scores of the Movement ABC-2 and full-scale IQ, and between the percentiles for the total scores of the Movement ABC-2 and WISC-IV indexes were calculated using Pearson correlations. Associations between DCD and background characteristics were studied using logistic regression analysis. Differences in the full-scale IQ and indexes between children with DCD and children without motor impairment were studied using two-sample t-test. The associations between motor outcome (DCD and children without motor impairment), cognitive outcome (full-scale IQ and indexes), and background characteristics birth weight, gestational age, and mother's and father's education) were studied using the multiple linear regression model. The background characteristics were chosen a priori.

If up to three dimensions were missing from the 17D, multiple imputation was used to replace missing values with one value, as suggested by the instrument's home page (http://www.15d-instrument.net/rmd) in order to calculate the 17D total score. If more than three dimensions were missing, the questionnaire was not used in the analyses. Differences in the 17D scores between the groups were studied using Mann-Whitney U Test. The statistical analyses were carried out using a 9.4 version of SAS Institute Inc. (Cary, NC, USA) for Windows. P-values of <0.05 were considered statistically significant.

RESULTS

A total of 170 very preterm children were followed until 11 years of age. The follow-up rate was 77.6% (out of participants). The background characteristics are shown in *Table 1*. No statistically significant differences were found between the background characteristics of the study children and the drop-outs.

Motor development

All the very preterm born children, including those with full-scale IQ <70, were able to follow the given instructions without any adaptations of test items and completed the Movement ABC-2. Accordingly, they were included in the analyses regarding DCD as suggested according to the recent European Academy of Childhood Disability recommendations[12]. There were nine (5.3%) children with CP who were assessed at 11 years of age; they were excluded from the analyses regarding the Movement ABC-2.

Of all the 161 very preterm born children without CP, one child did not complete the Movement ABC-2. A total of 142 (88.8%) had a total test score >5th percentile. Of these children, 12 (8.5%) had their score between 5th and 15th percentile in the Movement ABC-2 indicating a risk for motor problems. There were 18 children (11.3%) with a total test score ≤5th percentile in the Movement ABC-2; these children were denoted having DCD after confirming with the Touwen neurological examination that they did not have such neurological findings or other neurological disorders which could explain their poor performance. Twelve of the children with DCD were born extremely preterm (<28 gestational weeks) and/or with extremely low birth weight (≤1000g), representing 18.2% of all (n=66) extremely preterm and/or extremely low birth weight children. All but one of the children with DCD were boys. Of the other background characteristics shown in *Table 1*, lower

gestational age (p=0.04), bronchopulmonary dysplasia (p=0.04), sepsis (p=0.04), and major brain pathologies in the magnetic resonance imaging at term age (p=0.02) were associated with DCD.

Cognitive development

The mean value (SD, [min, max]) of the full-scale IQ for the whole very preterm study cohort (n=170) was 88.3 (17.0 [40.0, 131.0]). The mean value for the verbal comprehension was 90.3 (14.8, [46.0, 122.0]), for the perceptual reasoning 92.0 (17.1 [40.0, 122.0]), for the working memory 92.6 (16.3 [46.0, 133.0]) and for the processing speed 93.9 (17.4 [47.0, 153.0]). Of all the 161 children without CP, 89 (55.3%) performed within the average range (full-scale IQ ≥90), 34 (21.1%) had low average performance (full-scale IQ ≥80-89), 25 (15.5%) had borderline cognitive development (full-scale IQ ≥70-79), and 13 (8.1%) had severe cognitive impairment (full-scale IQ <70). The mean values of the full-scale IQ and its four indexes are shown by categories of motor outcome in *Table 2*.

The Movement ABC-2 scores in very preterm children without CP correlated positively with full-scale IQ (r=0.2, p=0.006), working memory index (r=0.3, p<0.001), processing speed index (r=0.2, p=0.03), and perceptual reasoning (r=0.2, p=0.03). The scatter plot of the full-scale IQ and the Movement ABC-2 is shown in *Figure 2*. Children with DCD had lower full-scale IQ than children without motor impairment (mean 76.8 vs. 91.6) (p<0.001). Similarly, children with DCD scored lower than children without motor impairment in all indexes as shown in *Table 2*. The results remained statistically significant after adjusting with birth weight, gestational age, and mother's and father's education.

Health-related quality of life

A total of 167 (98.2%) of the very preterm born children completed the 17D questionnaire as required in the instrument's guidelines. There were no statistically significant correlations between

the Movement ABC-2 and the 17D (r=0.1, p=0.06) nor between the full-scale IQ and the 17D (r=0.07, p=0.4). However, children with DCD had worse self-experienced HRQoL compared with children without DCD (0.93 vs. 0.96, p=0.03). Children with DCD showed more problems than children without DCD on the dimensions considering vision (0.96 vs. 0.99, p=0.008), hearing (0.92 vs. 0.98, p=0.01), and speech (0.96 vs. 0.99, p=0.007). The HRQoL of children with CP did not differ from the HRQoL of children without CP (0.94 vs. 0.96, p=0.6), nor did the HRQoL in children with severe cognitive impairment (full-scale IQ<70) from the children without cognitive impairment (0.93 vs. 0.96, p=0.2). This cohort of very preterm children reported better self-experienced HRQoL compared to Finnish population based normative results[32] (p<0.001). Very preterm children showed less problems than the normative population on the dimensions considering sleeping (p=0.02), discomfort and symptoms (p<0.001), depression (p<0.001), vitality (p=0.02), appearance (p=0.03), friends (p=0.01), and concentration (p=0.001).

DISCUSSION

This study showed that DCD is more common (11%) in 11-year-old very preterm children compared to population norms (5%). Children with DCD had adverse cognitive development than children without motor impairment. Moreover, children with DCD reported lower HRQoL than children without motor impairment. However, the HRQoL was higher in this study cohort of very preterm children than in Finnish norm population.

The finding of a high rate of DCD in very preterm born children in early adolescence is parallel to the recently reported rising trend of non-CP motor impairments in extremely preterm born children at the age of 6.5 and 8 years[7,18]. The rate of DCD in the extremely preterm born children of this PIPARI Study cohort was 18%, while two recent studies have reported DCD rates of 26-37% in extremely preterm populations[7,18]. One of the studies used a cut-off based on their control group, but reported that if the normative cut-offs had been used the rate of DCD would have been 12.5%. Some studies have reported the prevalence of DCD as being higher in boys[7,12], while others have shown no significant difference in the DCD prevalence in boys and girls[18]. In the present study, all but one of the children with DCD were boys. However, the small number of children with DCD did not enable reliable statistical analysis regarding gender.

A positive correlation between motor outcome and cognitive development in very preterm born children was found. Children with DCD had lower score in full-scale IQ and in all indexes (verbal comprehension, perceptual reasoning, working memory, and processing speed) compared with children without motor impairment. This is in line with previous studies that have reported lower full-scale IQ and processing speed in very preterm children with DCD at 5 years of age[19] and lower perceptual reasoning and processing speed in extremely preterm born children with DCD at 6.5 years of age[18]. According to our results, DCD might indicate also problems in cognitive

development at 11 years of age in children born very preterm. Lower motor scores accumulated among boys in the present study. Future research may expand current findings about possible mechanisms leading to vulnerability according to gender.

This study showed lower self-experienced HRQoL in very preterm born children with DCD compared to very preterm born children without motor impairment in early adolescence. The affected domains were vision, hearing, and speech. A previous review using various instruments suggested difficulties concerning fine motor skills (and causing difficulty e.g. with brushing teeth, washing hair, dressing up and using knife and fork) and social skills (causing e.g. loneliness and spending more time alone)[34]. However, comparing different instruments should be treated with caution. Self-experienced HRQoL at 11 years of age was better in our study cohort of children born very preterm compared to the test normative at the same age in the Finnish population. This is an unexpected finding as very preterm children have many impairments potentially lowering their HRQoL. One explanation might be that our cohort of very preterm children were born in the 2000s, while the data collection for HRQoL norms was performed in the 1990s. However, we are not aware of differences in general health outcomes in 1990s and 2000s. In any case, good HRQoL in very preterm children at 11 years of age is reassuring information for families with a preterm infant.

The strength of this study was a relatively high follow-up rate from birth to 11 years of age. The examinations were performed with the latest version of the Movement ABC-2, and a thorough Touwen neurological examination was used to support the diagnosis of DCD. A possible limitation was that the motor assessments were not done repeatedly as suggested in the latest European Academy of Childhood Disability recommendations[12]. However, these new guidelines were not available during the data collection. Therefore, we chose to use the strict cut-off of the 5th percentile to define DCD. A limitation of this study was the lack of a control group. Although the sample size

of the whole study group was satisfactory, the total number of children with DCD and CP were small, which restricts the power of the statistical analysis concerning these groups and generalizability of the results.

CONCLUSIONS

This study supports previous findings that even though more preterm born infants survive without CP they still have an increased risk for DCD. Children with DCD showed lower cognitive performance than children without DCD. It is important to recognize motor problems early to provide interventions and support services needed and to provide cognitive assessments with a low threshold. The HRQoL of very preterm children was to a large extent good but did however differ between children with DCD and those without motor impairment.

Acknowledgements:
For the collaboration regarding the 17D questionnaire: Marjo Apajasalo and Harri Sintonen.
The PIPARI Study Group: Mikael Ekblad, MD, PhD; Satu Ekblad, RN; Eeva Ekholm, MD, PhD; Annika Eurola, MD; Leena Haataja, MD, PhD; Mira Huhtala, MD, PhD; Jere Jaakkola, BM; Pentti Kero, MD, PhD; Riikka Korja, PhD; Katri Lahti, MD; Helena Lapinleimu, MD, PhD; Liisa Lehtonen, MD, PhD; Tuomo Lehtonen, MD; Marika Leppänen, MD, PhD; Annika Lind, PhD; Jaakko Matomäki, MSc; Jonna Maunu, MD, PhD; Petriina Munck PhD; Laura Määttänen, MD; Pekka Niemi, PhD; Anna Nyman, PhD; Pertti Palo, MD, PhD; Riitta Parkkola, MD, PhD; Liisi Ripatti, MD, PhD; Päivi Rautava, MD, PhD; Katriina Saarinen, Physiotherapist; Virva Saunavaara, PhD; Sirkku Setänen, MD, PhD; Matti Sillanpää, MD, PhD; Suvi Stolt, PhD; Sanna Sutinen, BM; Päivi Tuomikoski-Koiranen, RN; Timo Tuovinen, BA; Karoliina Uusitalo, MD; Anniina Väliaho, MA; Milla Ylijoki, MD, PhD.

Funding source: All phases of this study were supported by a grant from the Arvo and Lea Ylppö Foundation, the Emil Aaltonen Foundation, the Finnish Medical Foundation, the Finnish Cultural Foundation, the South-Western Finnish Foundation of Neonatal Research, the Turku University Research Foundation, and the Yrjö Jahnsson Foundation.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Potential Conflicts of Interest: The authors have no conflicts of interest to disclose.

Clinical Trial Registration: The PIPARI study has not been registered as clinical trial since it is not an intervention study.

References

1. Platt MJ, Cans C, Johnson A, et al. Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study. *Lancet*. 2007;369(9555):43-50. doi:10.1016/S0140-6736(07)60030-0
2. Groenendaal F, Termote J, Van Der Heide-Jalving M, Van Haastert I, De Vries L. Complications affecting preterm neonates from 1991 to 2006: What have we gained? *Acta Paediatr Int J Paediatr*. 2010;99(3):354-358. doi:10.1111/j.1651-2227.2009.01648.x
3. Sellier E, Platt MJ, Andersen GL, et al. Decreasing prevalence in cerebral palsy: A multi-site European population-based study, 1980 to 2003. *Dev Med Child Neurol*. 2016;58(1):85-92. doi:10.1111/dmcn.12865
4. Fawke J. Neurological outcomes following preterm birth. *Semin Fetal Neonatal Med*. 2007;12(5):374-382. doi:10.1016/j.siny.2007.06.002
5. Guerrot A-M, Chadie A, Torre S, et al. Compared outcomes of very preterm infants born in 2000 and 2005. *Acta Paediatr*. 2012;101(7):731-735. doi:10.1111/j.1651-2227.2012.02678.x
6. Holsti A, Adamsson M, Serenius F, H??ggl??f B, Farooqi A. Two-thirds of adolescents who received active perinatal care after extremely preterm birth had mild or no disabilities. *Acta Paediatr*. 2016;105(11):1288-1297. doi:10.1111/apa.13499
7. Spittle AJ, Cameron K, Doyle LW, Cheong JL. Motor impairment trends in extremely preterm children: 1991-2005. *Pediatrics*. 2018. doi:10.1542/peds.2017-3410
8. Pascal A, Govaert P, Oostra A, Naulaers G, Ortibus E, Van den Broeck 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. doi:10.1111/dmcn.13675
9. 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;352(1):9-19. doi:10.1056/NEJMoa041367
10. Anderson PJ. Neuropsychological outcomes of children born very preterm. *Semin Fetal Neonatal Med*. 2014;19(2):90-96. doi:10.1016/j.siny.2013.11.012
11. Nyman A, Korhonen T, Munck P, Parkkola R, Lehtonen L, Haataja L. Factors affecting the cognitive profile of 11-year-old children born very preterm. *Pediatr Res*. 2017;82(2):324-332. doi:10.1038/pr.2017.64
12. Blank R, Barnett AL, Cairney J, et al. International clinical practice recommendations on the definition, diagnosis, assessment, intervention, and psychosocial aspects of developmental coordination disorder. *Dev Med Child Neurol*. 2019. doi:10.1111/dmcn.14132
13. Brown-Lum M, Zwicker JG. Brain Imaging Increases Our Understanding of Developmental Coordination Disorder: a Review of Literature and Future Directions. *Curr Dev Disord Reports*. 2015;2(2):131-140. doi:10.1007/s40474-015-0046-6
14. Zwicker JG, Missiuna C, Harris SR, Boyd LA. Developmental coordination disorder: A review and update. *Eur J Paediatr Neurol*. 2012;16(6):573-581. doi:10.1016/j.ejpn.2012.05.005
15. Ferrari F, Gallo C, Pugliese M, et al. Preterm birth and developmental problems in the preschool age. Part I: Minor motor problems. *J Matern Neonatal Med*. 2012. doi:10.3109/14767058.2012.696164
16. Setänen S, Lehtonen L, Parkkola R, et al. The motor profile of preterm infants at 11 y of age. *Pediatr Res*. 2016;80(3). doi:10.1038/pr.2016.90
17. Harrowell I, Hollén L, Lingam R, Emond A. The impact of developmental coordination disorder on educational achievement in secondary school. *Res Dev Disabil*. 2018. doi:10.1016/j.ridd.2017.10.014
18. 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;172(8):765-774. doi:10.1001/jamapediatrics.2018.1394

19. Van Hus JW, Potharst ES, Jeukens-Visser M, Kok JH, Van Wassenaer-Leemhuis AG. Motor impairment in very preterm-born children: Links with other developmental deficits at 5 years of age. *Dev Med Child Neurol*. 2014;56(6):587-594. doi:10.1111/dmcn.12295
20. Huhtala M, Korja R, Rautava L, et al. Health-related quality of life in very low birth weight children at nearly eight years of age. *Acta Paediatr*. 2016;105(1):53-59. doi:10.1111/apa.13241
21. Natalucci G, Bucher HU, Von Rhein M, Borradori Tolsa C, Latal B, Adams M. Population based report on health related quality of life in adolescents born very preterm. *Early Hum Dev*. 2017;104:7-12. doi:10.1016/j.earlhumdev.2016.11.002
22. Zwicker JG, Harris SR. Quality of life of formerly preterm and very low birth weight infants from preschool age to adulthood: a systematic review. *Pediatrics*. 2008;121(2):e366-76. doi:10.1542/peds.2007-0169
23. Karras HC, Morin DN, Gill K, Izadi-Najafabadi S, Zwicker JG. Health-related quality of life of children with Developmental Coordination Disorder. *Res Dev Disabil*. 2018;(August 2017):1-11. doi:10.1016/j.ridd.2018.05.012
24. Dewey D, Volkovinskaia A. Health-related quality of life and peer relationships in adolescents with developmental coordination disorder and attention-deficit-hyperactivity disorder. *Dev Med Child Neurol*. 2018:711-718. doi:10.1111/dmcn.13753
25. Himmelmann K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995-1998. *Acta Paediatr Int J Paediatr*. 2005. doi:10.1080/08035250410023313
26. Henderson S, Sugden D. The movement assessment battery for children. *Phys Ther*. 1992;23:286-294. doi:10.1111/ppe.12025
27. Henderson S, Sugden D, Barnett A. *Movement Assessment Battery for Children (Examiner's Manual)*. London: Pearson Assessment; 2007.
28. Touwen BCL. *The Examination of the Child with Minor Neurological Dysfunction*.; 1979.
29. Hadders-Algra M. *The Neurological Examination of the Child With Minor Neurological Dysfunction, 3rd Edn.* London: Mac Keith Press; 2010.
30. Wechsler D. *Wechsler Intelligence Scale for Children -IV. Käsikirja I. Esitys Ja - Pisteytysohjeet (Handbook I. Administration and Scoring)*. Jyväskylä Psykologien Kustannus; 2011.
31. Wechsler D. *Wechsler Intelligence Scale for Children -IV. Käsikirja II. Teoriatausta, Standardointi Ja Tulkinta (Handbook II. Theoretical Background, Standardization and Interpretation)*. Jyväskylä Psykologien Kustannus; 2011.
32. Apajasalo M, Rautonen J, Holmberg C, et al. Quality of life in pre-adolescence: A 17-dimensional health-related measure (17D). *Qual Life Res*. 1996;5(6):532-538. doi:10.1007/BF00439227
33. Apajasalo M, Rautonen J, Holmberg C, et al. 17D. http://www.15d-instrument.net/16d-and-17d/17d/.
34. Zwicker JG, Harris SR, Klassen AF. Quality of life domains affected in children with developmental coordination disorder: A systematic review. *Child Care Health Dev*. 2013. doi:10.1111/j.1365-2214.2012.01379.x

Table 1. Background characteristics of the 11-year-old children (n=170) born at very low gestational age (<32 weeks) or with a very low birth weight (≤1500g).

Characteristics	
Gestational age, mean (SD) [min, max], wk	29.1 (2.7) [23.0, 35.9]
Birth weight, mean (SD) [min, max], g	1134.4 (315.3) [400.0, 2120.0]
Small for gestational age (<-2 SD), n (%)	56 (32.9)
Male, n (%)	94 (55.3)
Caesarean section, n (%)	101 (59.4)
Bronchopulmonary dysplasia, n (%)	22 (12.9)
Operated necrotizing enterocolitis, n (%)	7 (4.2)
Sepsis, n (%)	30 (17.7)
Laser-treated retinopathy of prematurity, n (%)	4 (2.4)
Brain magnetic resonance imaging at term age, (data missing for five children)*	
Normal findings, n (%)	96 (58.2)
Minor pathologies, n (%)	27 (16.4)
Major pathologies, n (%)	42 (25.5)
Mother's education, (data missing for two children)	
≤12 years, n (%)	61 (36.3)
>12 years, n (%)	107 (63.7)
Father's education, (data missing for four children)	
≤12 years, n (%)	110 (66.3)
>12 years, n (%)	56 (33.7)

*The specific MRI protocol and details about the classification of the findings have been previously described by Setänen et al. (Setänen S, Haataja L, Parkkola R, Lind A, Lehtonen L. Predictive value of neonatal brain MRI on the neurodevelopmental outcome of preterm infants by 5 years of age. *Acta Paediatr*. 2013. doi:10.1111/apa.12191)

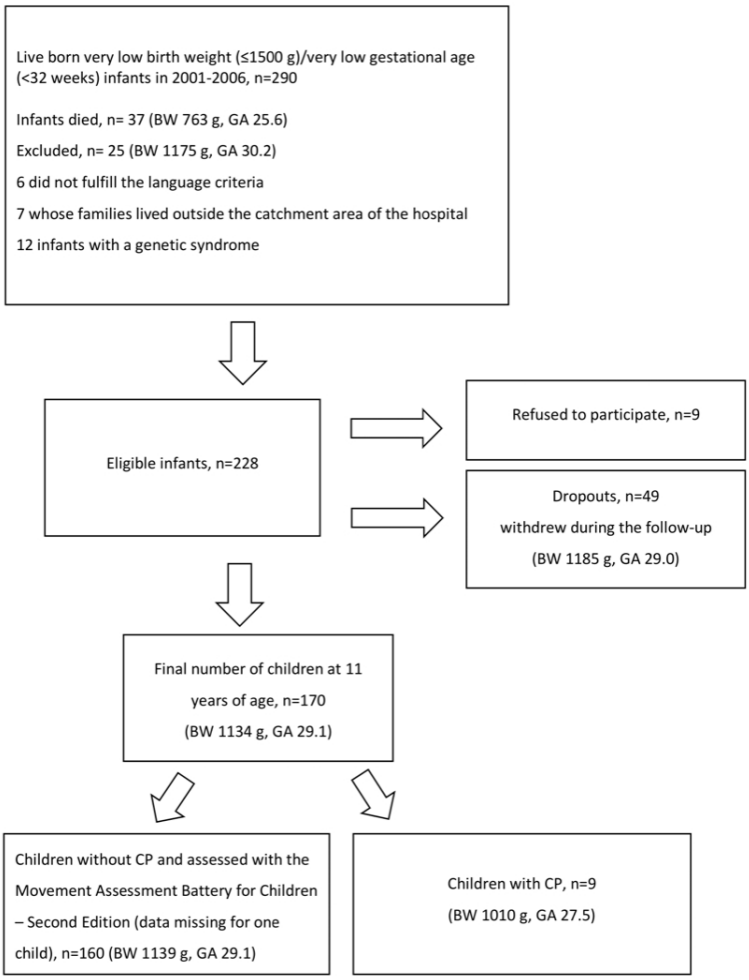
Table 2. Cognitive outcome and health-related quality of life are shown in 11-year-old very preterm children with cerebral palsy (CP) and according to the performance in Movement Assessment Battery for Children in children without CP. The mean values (SD), [minimum, maximum] of full-scale intelligence quotient and its four indexes are shown. The outcomes are compared between children with DCD and children without motor impairment (two-sample t-test).

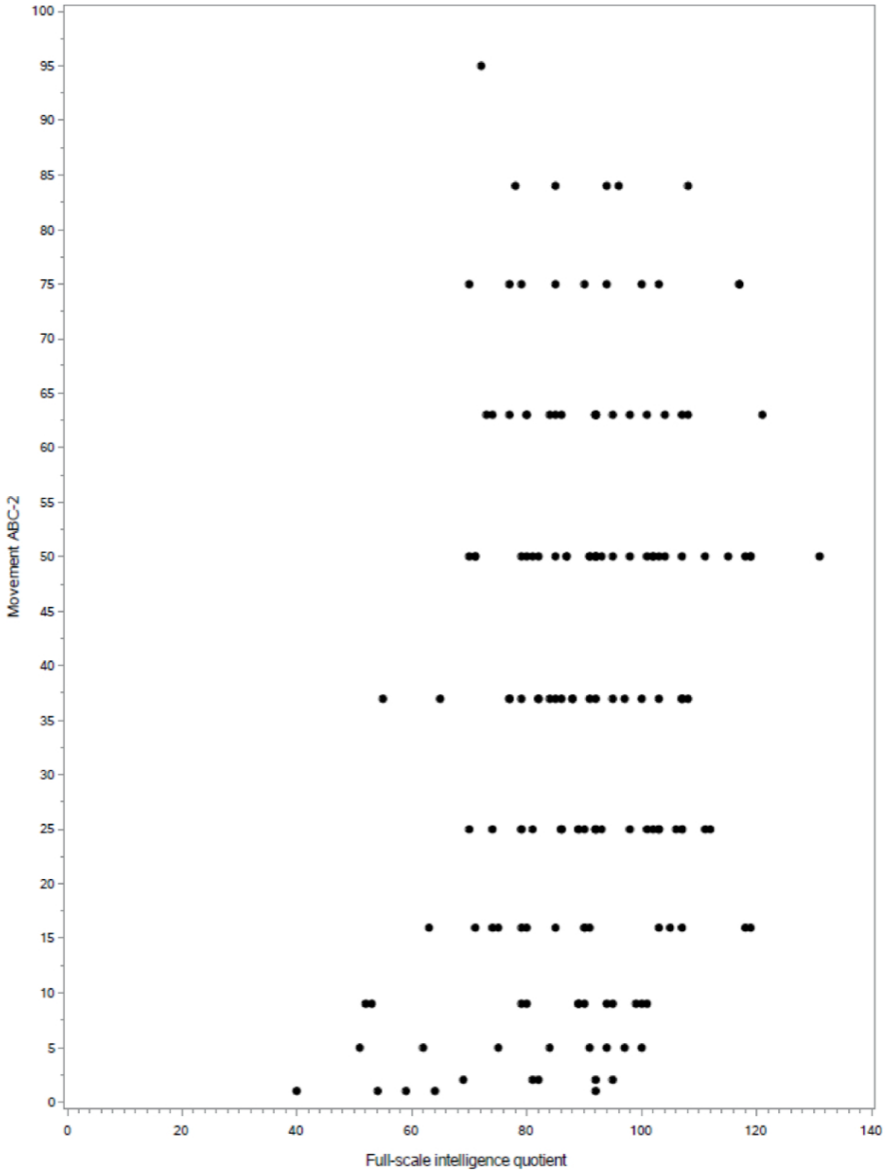
	CP, n=9	DCD, ≤5th percentile, n=18	Children without motor impairment, >5 percentile, n=142	P-value
Full-scale intelligence quotient	62.4 (22.8) [40.0, 97.0]	76.8 (18.2) [40.0, 100.0]	91.6 (14.3) [52.0, 131.0]	<0.001*
Verbal comprehension	75.1 (21.1) [46.0, 98.0]	83.8 (16.3) [46.0, 108.0]	92.1 (13.4) [60.0, 122.0]	0.02*
Perceptual reasoning	64.8 (23.1) [40.0, 100.0]	85.7 (17.9) [51.0, 109.0]	94.8 (14.6) [62.0, 122.0]	0.02*
Working memory	77.0 (20.5) [46.0, 109.0]	79.2 (13.9) [46.0, 97.0]	95.4 (15.0) [55.0, 133.0]	<0.001*
Processing speed	72.4 (21.4) [47.0, 106.0]	83.3 (19.4) [47.0, 118.0]	96.5 (15.5) [56.0, 153.0]	0.001*

*The results remained statistically significant after adjusting with birth weight, gestational age, and mother's and father's education.

Figure 1.
Flow chart of the participants, mean of gestational ages (GA) in weeks and birth weights (BW).

Figure 2. The scatter plot of the full-scale intelligence quotient and percentiles for the total scores of the Movement Assessment Battery for Children – Second Edition (Movement ABC-2) at 11 years of age in children born very low birth weight (≤1500g) or very low gestational age (<32 weeks).


Live born very low birth weight (≤1500 g)/very low gestational age (<32 weeks) infants in 2001-2006, n=290
Infants died, n= 37 (BW 763 g, GA 25.6)
Excluded, n= 25 (BW 1175 g, GA 30.2)
6 did not fulfill the language criteria
7 whose families lived outside the catchment area of the hospital
12 infants with a genetic syndrome
Eligible infants, n=228
Refused to participate, n=9
Dropouts, n=49
withdrew during the follow-up
(BW 1185 g, GA 29.0)
Final number of children at 11 years of age, n=170
(BW 1134 g, GA 29.1)
Children without CP and assessed with the Movement Assessment Battery for Children – Second Edition (data missing for one child), n=160 (BW 1139 g, GA 29.1)
Children with CP, n=9
(BW 1010 g, GA 27.5)


Movement ABC-2
Full-scale intelligence quotient
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
0
20
40
60
80
100
120
140

BMJ Paediatrics Open

Preterm children's developmental coordination disorder, cognition and quality of life - a prospective cohort study

Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2019-000633.R1
Article Type:	Original research
Date Submitted by the Author:	16-Jan-2020
Complete List of Authors:	Uusitalo, Karoliina; University of Turku, Pediatric Neurology; Turku University Hospital Haataja, Leena; University of Helsinki, Pediatric Neurology; Helsinki University Hospital, Children's Hospital, Pediatric Research Center Nyman, Anna; University of Turku, Psychology Ripatti, Liisi; Turku University Hospital, Pediatric Surgery Huhtala, Mira; Turku University Hospital, Oncology and Radiotherapy Rautava, Päivi; University of Turku, Public Health; Clinical Research Center Lehtonen, Prof Liisa; University of Turku, Pediatrics; Turku University Hospital, Pediatrics Parkkola, Riitta; University of Turku, Radiology; Turku PET Centre Lahti, Katri; University of Turku, Pediatric neurology; Turku University Hospital Koivisto, Mari; University of Turku Setänen, Sirkku; Uppsala Universitet, Women's and Children's Health; University of Turku, Pediatric Neurology
Keywords:	Neurodevelopment, Outcomes research, Neonatology

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Preterm children's developmental coordination disorder, cognition and quality of life - a prospective cohort study

Karoliina Uusitalo[a,b], MD, Leena Haataja[c], MD, PhD, Anna Nyman[d], PhD, Liisi Ripatti[e], MD, PhD, Mira Huhtala[f], MD, PhD, Päivi Rautava[g,h], MD, PhD, Liisa Lehtonen[b,i], MD, PhD, Riitta Parkkola[b,j], MD, PhD, Katri Lahti[a,b], MD, Mari Koivisto[h], MSc, Sirkku Setänen[a,b,k], MD, PhD, on behalf of the PIPARI Study Group

Affiliations: [a]Department of Pediatric Neurology, University of Turku, Turku, Finland; [b]Turku University Hospital, Turku, Finland; [c]Department of Pediatric Neurology, Children's Hospital, Pediatric Research Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [d]Department of Psychology, University of Turku, Turku, Finland; [e]Department of Pediatric Surgery, Turku University Hospital, Turku, Finland, [f]Department of Oncology and Radiotherapy, Turku University Hospital, Turku, Finland, [g]Department of Public Health, University of Turku, Turku, Finland; [h]Clinical Research Centre, Turku, Finland, [i]Department of Pediatrics, University of Turku, Turku, Finland; [j]Department of Radiology, and Turku PET Center, University of Turku; [k]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

Address correspondence to: Sirkku Setänen, Department of Women's and Children's Health, Uppsala University, Akademiska sjukhuset, 751 85 Uppsala, Uppsala, Sweden. Email: sirkku.setanen@kbh.uu.se

Word count: 2724

Abbreviations:
CP – cerebral palsy
DCD – developmental coordination disorder
IQ – intelligence quotient
HRQoL – health-related quality of life
Movement ABC-2 – Movement Assessment Battery for Children – Second Edition
WISC-IV – Wechsler Intelligence Scale for Children – Fourth Edition
17D – 17-dimensional illustrated questionnaire

What is known about this topic:

- The incidence of cerebral palsy has decreased in children born very preterm.
- Children born very preterm still have an increased risk for developmental coordination disorder (DCD).
- DCD may co-occur with cognitive dysfunction and lower health-related quality of life (HRQoL).

What this study adds:

- Very preterm born children with DCD had adverse cognitive development and self-experienced HRQoL compared with preterm children without motor impairment.
- This group of very preterm born children reported better HRQoL in comparison with Finnish norms.

Contributors' Statement Page

Dr Uusitalo collected the data, drafted the initial manuscript, and revised the manuscript.

Prof Haataja and Prof Lehtonen conceptualized and designed the study, designed the data collection instrument, supervised the data collection, revised the manuscript, and critically reviewed the study for its intellectual content.

PhD Nyman collected data, revised the manuscript and reviewed the manuscript for its intellectual content.

Dr Huhtala, Dr Ripatti and Prof Rautava revised the manuscript, and critically reviewed the study for its intellectual content, ensured that accuracy of any part of the work are appropriately investigated and resolved, and moreover, they were the specialists on HRQoL-testing.

Prof Parkkola supervised the data collection, revised the manuscript, and critically reviewed the study for its intellectual content.

Dr Lahti collected data, and revised the manuscript and reviewed the manuscript for its intellectual content.

Mrs Koivisto performed the statistical analysis of the data, and revised and reviewed the manuscript for its intellectual content.

Dr Setänen designed the study, collected data, revised the manuscript, and critically reviewed the study for its intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Objective: To evaluate the rate of developmental coordination disorder (DCD), its correlation to cognition and self-experienced health-related quality of life (HRQoL) in children born very preterm.

Design: Prospective follow-up study.

Setting: Regional population of very preterm children born in Turku University Hospital, Finland, in 2001-2006.

Patients: A total of 170 very preterm children were followed up until 11 years of age.

Main outcome measures: Motor and cognitive outcomes were evaluated using the Movement Assessment Battery for Children - Second Edition (Movement ABC-2) and the Wechsler Intelligence Scale for Children - Fourth Edition, respectively, and HRQoL using a 17-dimensional illustrated questionnaire (17D). The Touwen neurological examination was performed to exclude other neurological conditions affecting the motor outcome.

Results: Eighteen very preterm children (17 boys) (11.3%) had DCD, defined as the Movement ABC-2 total test score $\leq 5^{th}$ percentile. A positive correlation between motor and cognitive outcome ($r=0.22$, $p=0.006$) was found. Very preterm children with DCD had lower cognitive scores than those without DCD (full-scale intelligence quotient mean 76.8 vs. 91.6, $p=0.001$). Moreover, very preterm children with DCD reported lower HRQoL than very preterm children without motor impairment (17D mean 0.93 vs. 0.96, $p=0.03$). However, the HRQoL was higher in this group of very preterm children compared to population based normative test results ($p<0.001$).

Conclusions: DCD was more common in very preterm children at 11 years of age than in the general population. DCD associated with adverse cognitive development and self-experienced HRQoL. However, this group of very preterm children reported better HRQoL in comparison with Finnish norms.

INTRODUCTION

The incidence of cerebral palsy (CP) has decreased among children born very preterm[1–6]. However, the rate of non-CP motor impairments such as developmental coordination disorder (DCD) has not decreased[7], and children born preterm are still at increased risk for cognitive impairment compared to term peers[8–11].

DCD is defined as motor problems interfering with academic achieving or activities of daily living which cannot be explained by medical, neurological or cognitive impairment[12]. The etiology of DCD is multifactorial, and neuroimaging studies have shown alterations in the brain development and functioning in children with DCD[13–16]. The prevalence of DCD has been shown to vary from 5 to 6% in school-aged children and from 8 to 51% in those born preterm[8,12,17–19]. DCD has been shown to co-occur with developmental disorders such as social, behavioral and attention problems, and learning difficulties[12,17,20–22]. Nevertheless, data of the relationship between DCD and cognitive development in early adolescence is limited[22].

Severe neurodevelopmental impairments such as CP, cognitive impairment, hearing and visual impairment have been reported to associate with poorer self-experienced health-related quality of life (HRQoL) in school aged children born preterm, while those without these morbidities have reported HRQoL equal to peers[23,24]. The effect of preterm birth on HRQoL seems to be most significant in younger years and seems to decrease over time[25]. The impact of motor impairments such as DCD to HRQoL is not well known, and the reports have been controversial[26,27].

The aims of this study were to study the correlation between motor and cognitive development at 11 years of age in children born very preterm; and to study the effect of DCD on self-experienced HRQoL. We hypothesized that in very preterm children poorer motor outcome correlates with

adverse cognitive performance, and that DCD correlates with lower perceived HRQoL as compared to very preterm children without motor impairment.

METHODS

Participants

This prospective study is part of the PIPARI (The Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age) study of very preterm infants. The participants were born to Finnish- or Swedish-speaking families from January 2001 to December 2006 in Turku University Hospital, Finland. From 2001 to 2003 the inclusion criteria were birth weight ≤1500g and prematurity (<37 gestational weeks). From 2004, the inclusion criteria were broadened to all infants born ≤32 weeks of gestational age irrespective of the birth weight. The exclusion criteria were severe congenital anomalies or diagnosed syndrome affecting cognitive development. The flow chart of the participants is shown in Figure 1. The Ethics Review Committee of the Hospital District of South-West Finland approved the study protocol in 2000 and in 2012. Written informed consent for this follow-up study were provided by parents and children. This study was done without patient and public involvement.

Motor outcome

The diagnosis of CP was confirmed based on the classification proposed by Himmelmann et al.[28] after a systematic clinical follow-up by two years of corrected age by an experienced child neurologist. The motor outcome of the very preterm children without CP was evaluated at 11 years of age by one of the three physicians by using Movement Assessment Battery for Children – Second Edition (Movement ABC-2)[29,30]. The raw scores were converted into total standard scores and percentile scores according to the test manual, using the age band 3 (11 to 16 years) and the norms for 11-year-old children. A total test score >15th percentile indicated no movement difficulty, >5th to 15th percentile indicated risk of movement difficulties, and ≤5th percentile denoted DCD[30]. Touwen neurological examination was systematically used to confirm that there were no other neurological conditions such as muscle diseases affecting the motor development[30–32]. The

Movement ABC-2 examinations were video recorded in order to enable reassessment and to guarantee the comparability between examinations and no discrepancies were found.

Cognitive outcome

The cognitive development of the very preterm children at 11 years of age was assessed with the Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV), Finnish translation[33,34]. The assessments were performed either in Finnish or Swedish according to child's native language. Finnish assessments were performed by one of the two psychologists and Swedish speaking children were assessed by a native Swedish-speaking psychologist. General intelligence was measured with full-scale intelligence quotient (IQ), which consisted of the Verbal Comprehension Index, the Perceptual Reasoning Index, the Working Memory Index and the Processing Speed Index. The classification was based on the test manual[33,34]. The scores were classified as average if the full-scale IQ was ≥90, low average 80-89, and borderline 70-79. A full-scale IQ <70 was classified as severe cognitive impairment.

Health-related quality of life

The very preterm born children's self-experienced HRQoL at 11 years of age was evaluated using a generic self-assessment measure, a17-dimensional illustrated questionnaire (17D)[35]. It consisted of 17 multiple-choice questions of health and function. The domains were mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, school and hobbies, learning and memory, discomfort and symptoms, depression, distress, vitality, appearance, friends and concentration. Every domain had a five-level tick box functioning scale alternating from a perfect level to a severe dysfunction. The children completed the questionnaire by themselves or as an interview by the physician before the motor assessment. The relative weights of each dimension were defined in the instrument's home page[36]. The overall HRQoL was calculated from the health state descriptive system using

population-based preference or utility weights for 11-year-old healthy Finnish school children. The HRQoL score varied from zero (worst score, equals to death) to one (best score, equals complete health)[35].

Statistical Analysis

Difference in continuous background characteristics between very preterm study children and the drop-outs were studied using a two-sample t-test or a Wilcoxon two-sample test. For the categorical background characteristics, a chi-square test or Fisher's exact test were used. Correlations between the percentiles for the total scores of the Movement ABC-2 and full-scale IQ, and between the percentiles for the total scores of the Movement ABC-2 and WISC-IV indexes were calculated using Pearson correlations. Associations between DCD and background characteristics were studied using logistic regression analysis. Differences in the full-scale IQ and indexes between very preterm children with and without DCD were studied using two-sample t-test. The associations between motor outcome (very preterm children with and without DCD), cognitive outcome (full-scale IQ and indexes), and background characteristics birth weight, gestational age, and mother's and father's education) were studied using the multiple linear regression model. The background characteristics were chosen a priori.

If up to three dimensions were missing from the 17D, multiple imputation was used to replace missing values with one value, as suggested by the instrument's home page (http://www.15d-instrument.net/rmd) in order to calculate the 17D total score. If more than three dimensions were missing, the questionnaire was not used in the analyses. Differences in the 17D scores between the groups were studied using Mann-Whitney U Test. The statistical analyses were carried out using a 9.4 version of SAS Institute Inc. (Cary, NC, USA) for Windows. P-values of <0.05 were considered statistically significant.

RESULTS

A total of 170 very preterm children were followed until 11 years of age. The follow-up rate was 77.6% (out of participants). The background characteristics are shown in *Table 1*. No statistically significant differences were found between the background characteristics of the study children and the drop-outs.

Motor development

All the very preterm born children, including those with full-scale IQ <70, were able to follow the given instructions without any adaptations of test items and completed the Movement ABC-2. Accordingly, very preterm children with full-scale IQ <70 were included in the analyses regarding DCD as suggested according to the recent European Academy of Childhood Disability recommendations[12]. There were nine (5.3%) very preterm children with CP who were assessed at 11 years of age; they were excluded from the analyses regarding the Movement ABC-2.

Of all the 161 very preterm born children without CP, one child did not complete the Movement ABC-2. A total of 142 (88.8%) had a total test score >5th percentile. Of these very preterm children, 12 (8.5%) had their score between 5th and 15th percentile in the Movement ABC-2 indicating a risk for motor problems. There were 18 very preterm children (11.3%) with a total test score ≤5th percentile in the Movement ABC-2; these children were denoted having DCD after confirming with the Touwen neurological examination that they did not have such neurological findings or other neurological disorders which could explain their poor performance. Twelve of the very preterm children with DCD were born extremely preterm (<28 gestational weeks) and/or with extremely low birth weight (≤1000g), representing 18.2% of all (n=66) extremely preterm and/or extremely low birth weight children. All but one of the very preterm children with DCD were boys. Of the other background characteristics shown in *Table 1*, lower gestational age (p=0.04),

bronchopulmonary dysplasia (p=0.04), sepsis (p=0.04), and major brain pathologies in the magnetic resonance imaging at term age (p=0.02) were associated with DCD.

Cognitive development

The mean value (SD, [min, max]) of the full-scale IQ for the whole very preterm study cohort (n=170) was 88.3 (17.0 [40.0, 131.0]). The mean value for the verbal comprehension was 90.3 (14.8, [46.0, 122.0]), for the perceptual reasoning 92.0 (17.1 [40.0, 122.0]), for the working memory 92.6 (16.3 [46.0, 133.0]) and for the processing speed 93.9 (17.4 [47.0, 153.0]). Of all the 161 very preterm children without CP, 89 (55.3%) performed within the average range (full-scale IQ ≥90), 34 (21.1%) had low average performance (full-scale IQ ≥80-89), 25 (15.5%) had borderline cognitive development (full-scale IQ ≥70-79), and 13 (8.1%) had severe cognitive impairment (full-scale IQ <70). The mean values of the full-scale IQ and its four indexes are shown by categories of motor outcome in *Table 2*.

The Movement ABC-2 scores in very preterm children without CP correlated positively with full-scale IQ (r=0.2, p=0.006), working memory index (r=0.3, p<0.001), processing speed index (r=0.2, p=0.03), and perceptual reasoning (r=0.2, p=0.03). The scatter plot of the full-scale IQ and the Movement ABC-2 is shown in *Figure 2*. Very preterm children with DCD had lower full-scale IQ than very preterm children without motor impairment (mean 76.8 vs. 91.6) (p<0.001). Similarly, very preterm children with DCD scored lower than very preterm children without motor impairment in all indexes as shown in *Table 2.* The results remained statistically significant after adjusting with birth weight, gestational age, and mother's and father's education.

Health-related quality of life

A total of 167 (98.2%) of the very preterm born children completed the 17D questionnaire as

required in the instrument's guidelines. There were no statistically significant correlations between the Movement ABC-2 and the 17D (r=0.1, p=0.06) nor between the full-scale IQ and the 17D (r=0.07, p=0.4). However, very preterm children with DCD had worse self-experienced HRQoL compared with very preterm children without DCD (0.93 vs. 0.96, p=0.03). Very preterm children with DCD showed more problems than very preterm children without DCD on the dimensions considering vision (0.96 vs. 0.99, p=0.008), hearing (0.92 vs. 0.98, p=0.01), and speech (0.96 vs. 0.99, p=0.007). The HRQoL of very preterm children with CP did not differ from the HRQoL of very preterm children without CP (0.94 vs. 0.96, p=0.6), nor did the HRQoL in very preterm children with severe cognitive impairment (full-scale IQ<70) from the very preterm children without cognitive impairment (0.93 vs. 0.96, p=0.2). This cohort of very preterm children reported better self-experienced HRQoL compared to Finnish population based normative results[35] (p<0.001). Very preterm children showed less problems than the normative population on the dimensions considering sleeping (p=0.02), discomfort and symptoms (p<0.001), depression (p<0.001), vitality (p=0.02), appearance (p=0.03), friends (p=0.01), and concentration (p=0.001).

DISCUSSION

This study showed that DCD is more common (11%) in 11-year-old very preterm children compared to population norms (5%). Very preterm children with DCD had adverse cognitive development than very preterm children without motor impairment. Moreover, very preterm children with DCD reported lower HRQoL than very preterm children without DCD. However, the HRQoL was higher in this study cohort of very preterm children than in Finnish norm population.

The finding of a high rate of DCD in very preterm born children in early adolescence is parallel to the recently reported rising trend of non-CP motor impairments in extremely preterm born children at the age of 6.5 and 8 years[7,21]. The rate of DCD in the extremely preterm born children of this PIPARI Study cohort was 18%, while two recent studies have reported DCD rates of 26-37% in extremely preterm populations[7,21]. One of the studies used a cut-off based on their control group, but reported that if the normative cut-offs had been used the rate of DCD would have been 12.5%. Some studies have reported the prevalence of DCD as being higher in boys[7,12], while others have shown no significant difference in the DCD prevalence in boys and girls[21]. In the present study, all but one of the children with DCD were boys. However, the small number of children with DCD did not enable reliable statistical analysis regarding gender.

A positive correlation between motor outcome and cognitive development in very preterm born children was found. Very preterm children with DCD had lower score in full-scale IQ and in all indexes (verbal comprehension, perceptual reasoning, working memory, and processing speed) compared with very preterm children without motor impairment. This is in line with previous studies that have reported lower full-scale IQ and processing speed in very preterm children with DCD at 5 years of age[22] and lower perceptual reasoning and processing speed in extremely preterm born children with DCD at 6.5 years of age[21]. According to our results, DCD might indicate also

problems in cognitive development at 11 years of age in children born very preterm. Lower motor scores accumulated among very preterm boys in the present study. Future research may expand current findings about possible mechanisms leading to vulnerability according to gender.

This study showed lower self-experienced HRQoL in very preterm born children with DCD compared to very preterm born children without motor impairment in early adolescence. The affected domains were vision, hearing, and speech. A previous review using various instruments suggested difficulties concerning fine motor skills (and causing difficulty e.g. with brushing teeth, washing hair, dressing up and using knife and fork) and social skills (causing e.g. loneliness and spending more time alone)[37]. However, comparing different instruments should be treated with caution. Self-experienced HRQoL at 11 years of age was better in our study cohort of children born very preterm compared to the test normative at the same age in the Finnish population. This is an unexpected finding as very preterm children have many impairments potentially lowering their HRQoL. One explanation might be that our cohort of very preterm children were born in the 2000s, while the data collection for HRQoL norms was performed in the 1990s. However, we are not aware of differences in general health outcomes in 1990s and 2000s. In any case, good HRQoL in very preterm children at 11 years of age is reassuring information for families with a preterm infant.

The strength of this study was a relatively high follow-up rate from birth to 11 years of age. The examinations were performed with the latest version of the Movement ABC-2, and a thorough Touwen neurological examination was used to support the diagnosis of DCD. A possible limitation was that the motor assessments were not done repeatedly as suggested in the latest European Academy of Childhood Disability recommendations[12]. However, these new guidelines were not available during the data collection. Therefore, we chose to use the strict cut-off of the 5th percentile to define DCD. A limitation of this study was the lack of a control group. Although the sample size

of the whole study group was satisfactory, the total number of very preterm children with DCD and CP were small, which restricts the power of the statistical analysis concerning these groups and generalizability of the results.

CONCLUSIONS

This study supports previous findings that even though more preterm born infants survive without CP they still have an increased risk for DCD. Very preterm children with DCD showed lower cognitive performance than very preterm children without DCD. It is important to recognize motor problems early to provide interventions and support services needed and to provide cognitive assessments with a low threshold. The HRQoL of very preterm children was to a large extent good but did however differ between very preterm children with DCD and those without motor impairment.

Acknowledgements:
For the collaboration regarding the 17D questionnaire: Marjo Apajasalo and Harri Sintonen.
The PIPARI Study Group: Mikael Ekblad, MD, PhD; Satu Ekblad, RN; Eeva Ekholm, MD, PhD; Annika Eurola, MD; Leena Haataja, MD, PhD; Mira Huhtala, MD, PhD; Jere Jaakkola, BM; Pentti Kero, MD, PhD; Riikka Korja, PhD; Katri Lahti, MD; Helena Lapinleimu, MD, PhD; Liisa Lehtonen, MD, PhD; Tuomo Lehtonen, MD; Marika Leppänen, MD, PhD; Annika Lind, PhD; Jaakko Matomäki, MSc; Jonna Maunu, MD, PhD; Petriina Munck PhD; Laura Määttänen, MD; Pekka Niemi, PhD; Anna Nyman, PhD; Pertti Palo, MD, PhD; Riitta Parkkola, MD, PhD; Liisi Ripatti, MD, PhD; Päivi Rautava, MD, PhD; Katriina Saarinen, Physiotherapist; Virva Saunavaara, PhD; Sirkku Setänen, MD, PhD; Matti Sillanpää, MD, PhD; Suvi Stolt, PhD; Sanna Sutinen, BM; Päivi Tuomikoski-Koiranen, RN; Timo Tuovinen, BA; Karoliina Uusitalo, MD; Anniina Väliaho, MA; Milla Ylijoki, MD, PhD.

Funding source: All phases of this study were supported by a grant from the Arvo and Lea Ylppö Foundation, the Emil Aaltonen Foundation, the Finnish Medical Foundation, the Finnish Cultural Foundation, the South-Western Finnish Foundation of Neonatal Research, the Turku University Research Foundation, and the Yrjö Jahnsson Foundation.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Potential Conflicts of Interest: The authors have no conflicts of interest to disclose.

Clinical Trial Registration: The PIPARI study has not been registered as clinical trial since it is not an intervention study.

References

1. Platt MJ, Cans C, Johnson A, et al. Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study. *Lancet*. 2007;369(9555):43-50. doi:10.1016/S0140-6736(07)60030-0
2. Groenendaal F, Termote J, Van Der Heide-Jalving M, Van Haastert I, De Vries L. Complications affecting preterm neonates from 1991 to 2006: What have we gained? *Acta Paediatr Int J Paediatr*. 2010;99(3):354-358. doi:10.1111/j.1651-2227.2009.01648.x
3. Sellier E, Platt MJ, Andersen GL, et al. Decreasing prevalence in cerebral palsy: A multi-site European population-based study, 1980 to 2003. *Dev Med Child Neurol*. 2016;58(1):85-92. doi:10.1111/dmcn.12865
4. Fawke J. Neurological outcomes following preterm birth. *Semin Fetal Neonatal Med*. 2007;12(5):374-382. doi:10.1016/j.siny.2007.06.002
5. Guerrot A-M, Chadie A, Torre S, et al. Compared outcomes of very preterm infants born in 2000 and 2005. *Acta Paediatr*. 2012;101(7):731-735. doi:10.1111/j.1651-2227.2012.02678.x
6. Holsti A, Adamsson M, Serenius F, H??ggl??f B, Farooqi A. Two-thirds of adolescents who received active perinatal care after extremely preterm birth had mild or no disabilities. *Acta Paediatr*. 2016;105(11):1288-1297. doi:10.1111/apa.13499
7. Spittle AJ, Cameron K, Doyle LW, Cheong JL. Motor impairment trends in extremely preterm children: 1991-2005. *Pediatrics*. 2018. doi:10.1542/peds.2017-3410
8. Pascal A, Govaert P, Oostra A, Naulaers G, Ortibus E, Van den Broeck 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. doi:10.1111/dmcn.13675
9. 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;352(1):9-19. doi:10.1056/NEJMoa041367
10. Anderson PJ. Neuropsychological outcomes of children born very preterm. *Semin Fetal Neonatal Med*. 2014;19(2):90-96. doi:10.1016/j.siny.2013.11.012
11. Nyman A, Korhonen T, Munck P, Parkkola R, Lehtonen L, Haataja L. Factors affecting the cognitive profile of 11-year-old children born very preterm. *Pediatr Res*. 2017;82(2):324-332. doi:10.1038/pr.2017.64
12. Blank R, Barnett AL, Cairney J, et al. International clinical practice recommendations on the definition, diagnosis, assessment, intervention, and psychosocial aspects of developmental coordination disorder. *Dev Med Child Neurol*. 2019. doi:10.1111/dmcn.14132
13. Brown-Lum M, Zwicker JG. Brain Imaging Increases Our Understanding of Developmental Coordination Disorder: a Review of Literature and Future Directions. *Curr Dev Disord Reports*. 2015;2(2):131-140. doi:10.1007/s40474-015-0046-6
14. Biotteau M, Chaix Y, Blais M, Tallet J, Péran P, Albaret JM. Neural signature of dcd: A critical review of mri neuroimaging studies. *Front Neurol*. 2016. doi:10.3389/fneur.2016.00227
15. Lahti K, Saunavaara V, Munck P, et al. Diffusion tensor imaging is associated with motor outcomes of very preterm born children at 11 years of age. *Acta Paediatr Int J Paediatr*. 2019;(January):1-8. doi:10.1111/apa.15004
16. Dewey D, Thompson DK, Kelly CE, et al. Very preterm children at risk for developmental coordination disorder have brain alterations in motor areas. *Acta Paediatr Int J Paediatr*. 2019;108(9):1649-1660. doi:10.1111/apa.14786
17. Zwicker JG, Missiuna C, Harris SR, Boyd LA. Developmental coordination disorder: A review and update. *Eur J Paediatr Neurol*. 2012;16(6):573-581. doi:10.1016/j.ejpn.2012.05.005

18. Ferrari F, Gallo C, Pugliese M, et al. Preterm birth and developmental problems in the preschool age. Part I: Minor motor problems. *J Matern Neonatal Med*. 2012. doi:10.3109/14767058.2012.696164
19. Setänen S, Lehtonen L, Parkkola R, et al. The motor profile of preterm infants at 11 y of age. *Pediatr Res*. 2016;80(3). doi:10.1038/pr.2016.90
20. Harrowell I, Hollén L, Lingam R, Emond A. The impact of developmental coordination disorder on educational achievement in secondary school. *Res Dev Disabil*. 2018. doi:10.1016/j.ridd.2017.10.014
21. 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;172(8):765-774. doi:10.1001/jamapediatrics.2018.1394
22. Van Hus JW, Potharst ES, Jeukens-Visser M, Kok JH, Van Wassenaer-Leemhuis AG. Motor impairment in very preterm-born children: Links with other developmental deficits at 5 years of age. *Dev Med Child Neurol*. 2014;56(6):587-594. doi:10.1111/dmcn.12295
23. Huhtala M, Korja R, Rautava L, et al. Health-related quality of life in very low birth weight children at nearly eight years of age. *Acta Paediatr*. 2016;105(1):53-59. doi:10.1111/apa.13241
24. Natalucci G, Bucher HU, Von Rhein M, Borradori Tolsa C, Latal B, Adams M. Population based report on health related quality of life in adolescents born very preterm. *Early Hum Dev*. 2017;104:7-12. doi:10.1016/j.earlhumdev.2016.11.002
25. Zwicker JG, Harris SR. Quality of life of formerly preterm and very low birth weight infants from preschool age to adulthood: a systematic review. *Pediatrics*. 2008;121(2):e366-76. doi:10.1542/peds.2007-0169
26. Karras HC, Morin DN, Gill K, Izadi-Najafabadi S, Zwicker JG. Health-related quality of life of children with Developmental Coordination Disorder. *Res Dev Disabil*. 2018;(August 2017):1-11. doi:10.1016/j.ridd.2018.05.012
27. Dewey D, Volkovinskaia A. Health-related quality of life and peer relationships in adolescents with developmental coordination disorder and attention-deficit-hyperactivity disorder. *Dev Med Child Neurol*. 2018:711-718. doi:10.1111/dmcn.13753
28. Himmelmann K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995-1998. *Acta Paediatr Int J Paediatr*. 2005. doi:10.1080/08035250410023313
29. Henderson S, Sugden D. The movement assessment battery for children. *Phys Ther*. 1992;23:286-294. doi:10.1111/ppe.12025
30. Henderson S, Sugden D, Barnett A. *Movement Assessment Battery for Children (Examiner's Manual)*. London: Pearson Assessment; 2007.
31. Touwen BCL. *The Examination of the Child with Minor Neurological Dysfunction*.; 1979.
32. Hadders-Algra M. *The Neurological Examination of the Child With Minor Neurological Dysfunction, 3rd Edn.* London: Mac Keith Press; 2010.
33. Wechsler D. *Wechsler Intelligence Scale for Children -IV. Käsikirja I. Esitys Ja - Pisteytysohjeet (Handbook I. Administration and Scoring)*. Jyväskylä Psykologien Kustannus; 2011.
34. Wechsler D. *Wechsler Intelligence Scale for Children -IV. Käsikirja II. Teoriatausta, Standardointi Ja Tulkinta (Handbook II. Theoretical Background, Standardization and Interpretation)*. Jyväskylä Psykologien Kustannus; 2011.
35. Apajasalo M, Rautonen J, Holmberg C, et al. Quality of life in pre-adolescence: A 17-dimensional health-related measure (17D). *Qual Life Res*. 1996;5(6):532-538. doi:10.1007/BF00439227
36. Apajasalo M, Rautonen J, Holmberg C, et al. 17D. http://www.15d-instrument.net/16d-and-

17d/17d/.
37. Zwicker JG, Harris SR, Klassen AF. Quality of life domains affected in children with developmental coordination disorder: A systematic review. *Child Care Health Dev*. 2013. doi:10.1111/j.1365-2214.2012.01379.x

Table 1. Background characteristics of the 11-year-old children (n=170) born at very low gestational age (<32 weeks) or with a very low birth weight (≤1500g).

Characteristics	
Gestational age, mean (SD) [min, max], wk	29.1 (2.7) [23.0, 35.9]
Birth weight, mean (SD) [min, max], g	1134.4 (315.3) [400.0, 2120.0]
Small for gestational age (<-2 SD), n (%)	56 (32.9)
Male, n (%)	94 (55.3)
Caesarean section, n (%)	101 (59.4)
Bronchopulmonary dysplasia, n (%)	22 (12.9)
Operated necrotizing enterocolitis, n (%)	7 (4.2)
Sepsis, n (%)	30 (17.7)
Laser-treated retinopathy of prematurity, n (%)	4 (2.4)
Brain magnetic resonance imaging at term age, (data missing for five children)*	
Normal findings, n (%)	96 (58.2)
Minor pathologies, n (%)	27 (16.4)
Major pathologies, n (%)	42 (25.5)
Mother's education, (data missing for two children)	
≤12 years, n (%)	61 (36.3)
>12 years, n (%)	107 (63.7)
Father's education, (data missing for four children)	
≤12 years, n (%)	110 (66.3)
>12 years, n (%)	56 (33.7)

*The specific MRI protocol and details about the classification of the findings have been previously described by Setänen et al. (Setänen S, Haataja L, Parkkola R, Lind A, Lehtonen L. Predictive value of neonatal brain MRI on the neurodevelopmental outcome of preterm infants by 5 years of age. *Acta Paediatr*. 2013. doi:10.1111/apa.12191)

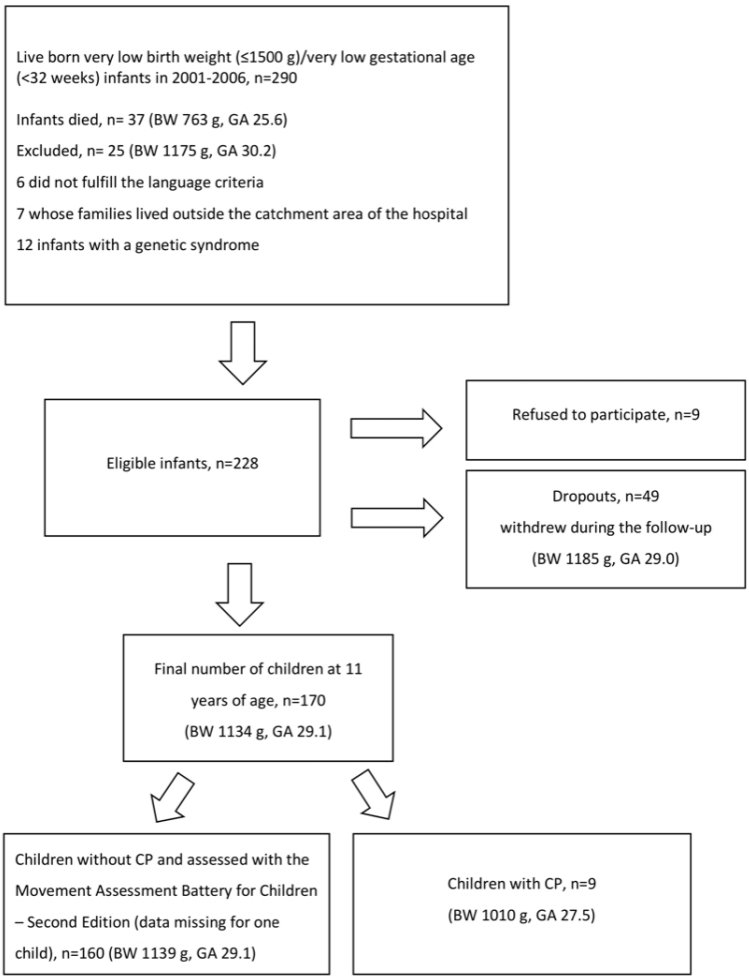
Table 2. Cognitive outcome and health-related quality of life are shown in 11-year-old very preterm children with cerebral palsy (CP) and according to the performance in Movement Assessment Battery for Children in children without CP. The mean values (SD), [minimum, maximum] of full-scale intelligence quotient and its four indexes are shown. The outcomes are compared between children with DCD and children without motor impairment (two-sample t-test).

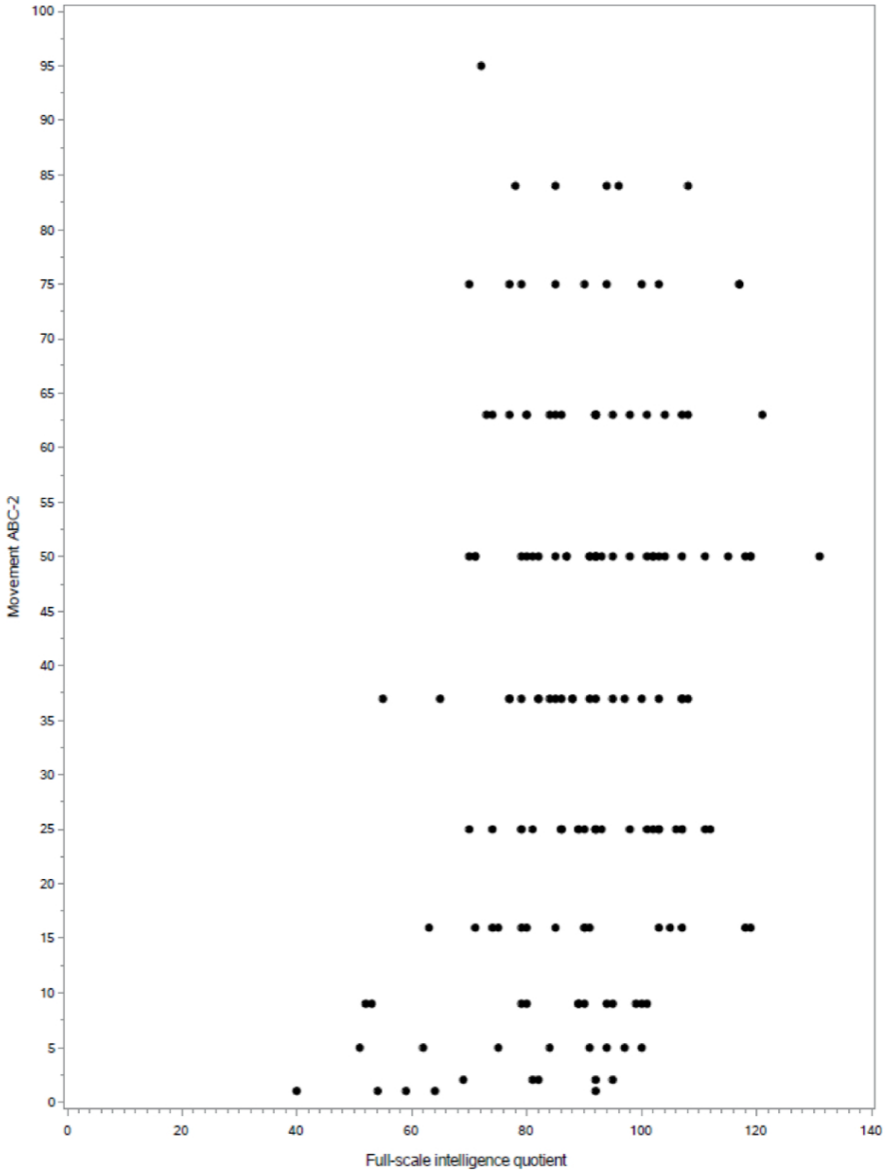
	CP, n=9	DCD, ≤5th percentile, n=18	Children without motor impairment, >5 percentile, n=142	P-value
Full-scale intelligence quotient	62.4 (22.8) [40.0, 97.0]	76.8 (18.2) [40.0, 100.0]	91.6 (14.3) [52.0, 131.0]	<0.001*
Verbal comprehension	75.1 (21.1) [46.0, 98.0]	83.8 (16.3) [46.0, 108.0]	92.1 (13.4) [60.0, 122.0]	0.02*
Perceptual reasoning	64.8 (23.1) [40.0, 100.0]	85.7 (17.9) [51.0, 109.0]	94.8 (14.6) [62.0, 122.0]	0.02*
Working memory	77.0 (20.5) [46.0, 109.0]	79.2 (13.9) [46.0, 97.0]	95.4 (15.0) [55.0, 133.0]	<0.001*
Processing speed	72.4 (21.4) [47.0, 106.0]	83.3 (19.4) [47.0, 118.0]	96.5 (15.5) [56.0, 153.0]	0.001*

*The results remained statistically significant after adjusting with birth weight, gestational age, and mother's and father's education.

Figure 1.
Flow chart of the participants, mean of gestational ages (GA) in weeks and birth weights (BW).

Figure 2. The scatter plot of the full-scale intelligence quotient and percentiles for the total scores of the Movement Assessment Battery for Children – Second Edition (Movement ABC-2) at 11 years of age in children born very low birth weight (≤1500g) or very low gestational age (<32 weeks).


Live born very low birth weight (≤1500 g)/very low gestational age (<32 weeks) infants in 2001-2006, n=290
Infants died, n= 37 (BW 763 g, GA 25.6)
Excluded, n= 25 (BW 1175 g, GA 30.2)
6 did not fulfill the language criteria
7 whose families lived outside the catchment area of the hospital
12 infants with a genetic syndrome
Eligible infants, n=228
Refused to participate, n=9
Dropouts, n=49
withdrew during the follow-up
(BW 1185 g, GA 29.0)
Final number of children at 11 years of age, n=170
(BW 1134 g, GA 29.1)
Children without CP and assessed with the Movement Assessment Battery for Children – Second Edition (data missing for one child), n=160 (BW 1139 g, GA 29.1)
Children with CP, n=9
(BW 1010 g, GA 27.5)


Movement ABC-2
Full-scale intelligence quotient
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
0
20
40
60
80
100
120
140

BMJ Paediatrics Open

Preterm children's developmental coordination disorder, cognition and quality of life - a prospective cohort study

Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2019-000633.R2
Article Type:	Original research
Date Submitted by the Author:	28-Feb-2020
Complete List of Authors:	Uusitalo, Karoliina; University of Turku, Pediatric Neurology; Turku University Hospital Haataja, Leena; University of Helsinki, Pediatric Neurology; Helsinki University Hospital, Children's Hospital, Pediatric Research Center Nyman, Anna; University of Turku, Psychology Ripatti, Liisi; Turku University Hospital, Pediatric Surgery Huhtala, Mira; Turku University Hospital, Oncology and Radiotherapy Rautava, Päivi; University of Turku, Public Health; Clinical Research Center Lehtonen, Prof Liisa; University of Turku, Pediatrics; Turku University Hospital, Pediatrics Parkkola, Riitta; University of Turku, Radiology; Turku PET Centre Lahti, Katri; University of Turku, Pediatric neurology; Turku University Hospital Koivisto, Mari; University of Turku Setänen, Sirkku; Uppsala Universitet, Women's and Children's Health; University of Turku, Pediatric Neurology
Keywords:	Neurodevelopment, Outcomes research, Neonatology

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Preterm children's developmental coordination disorder, cognition and quality of life - a prospective cohort study

Karoliina Uusitalo[a,b], MD, Leena Haataja[c], MD, PhD, Anna Nyman[d], PhD, Liisi Ripatti[e], MD, PhD, Mira Huhtala[f], MD, PhD, Päivi Rautava[g,h], MD, PhD, Liisa Lehtonen[b,i], MD, PhD, Riitta Parkkola[b,j], MD, PhD, Katri Lahti[a,b], MD, Mari Koivisto[h], MSc, Sirkku Setänen[a,b,k], MD, PhD, on behalf of the PIPARI Study Group

Affiliations: [a]Department of Pediatric Neurology, University of Turku, Turku, Finland; [b]Turku University Hospital, Turku, Finland; [c]Department of Pediatric Neurology, Children's Hospital, Pediatric Research Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [d]Department of Psychology, University of Turku, Turku, Finland; [e]Department of Pediatric Surgery, Turku University Hospital, Turku, Finland, [f]Department of Oncology and Radiotherapy, Turku University Hospital, Turku, Finland, [g]Department of Public Health, University of Turku, Turku, Finland; [h]Clinical Research Centre, Turku, Finland, [i]Department of Pediatrics, University of Turku, Turku, Finland; [j]Department of Radiology, and Turku PET Center, University of Turku; [k]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

Address correspondence to: Sirkku Setänen, Department of Women's and Children's Health, Uppsala University, Akademiska sjukhuset, 751 85 Uppsala, Uppsala, Sweden. Email: sirkku.setanen@kbh.uu.se

Word count: 3294

Abbreviations:
CP – cerebral palsy
DCD – developmental coordination disorder
IQ – intelligence quotient
HRQoL – health-related quality of life
Movement ABC-2 – Movement Assessment Battery for Children – Second Edition
WISC-IV – Wechsler Intelligence Scale for Children – Fourth Edition
17D – 17-dimensional illustrated questionnaire

What is known about this topic:

- The incidence of cerebral palsy has decreased in children born very preterm.
- Children born very preterm have an increased risk for developmental coordination disorder (DCD).
- DCD may co-occur with cognitive dysfunction and lower health-related quality of life (HRQoL).

What this study adds:

- DCD was still common in 11-year-old children born very preterm in 2000s.
- Children born very preterm with DCD had adverse cognitive development and lower self-experienced HRQoL compared with children born very preterm without motor impairment.

Contributors' Statement Page

Dr Uusitalo collected the data, drafted the initial manuscript, and revised the manuscript.

Prof Haataja and Prof Lehtonen conceptualized and designed the study, designed the data collection instrument, supervised the data collection, revised the manuscript, and critically reviewed the study for its intellectual content.

PhD Nyman collected data, revised the manuscript and reviewed the manuscript for its intellectual content.

Dr Huhtala, Dr Ripatti and Prof Rautava revised the manuscript, and critically reviewed the study for its intellectual content, ensured that accuracy of any part of the work are appropriately investigated and resolved, and moreover, they were the specialists on HRQoL-testing.

Prof Parkkola supervised the data collection, revised the manuscript, and critically reviewed the study for its intellectual content.

Dr Lahti collected data, and revised the manuscript and reviewed the manuscript for its intellectual content.

Mrs Koivisto performed the statistical analysis of the data, and revised and reviewed the manuscript for its intellectual content.

Dr Setänen designed the study, collected data, revised the manuscript, and critically reviewed the study for its intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Objective: To evaluate the rate of developmental coordination disorder (DCD), its correlation to cognition and self-experienced health-related quality of life (HRQoL) in children born very preterm.

Design: Prospective follow-up study.

Setting: Regional population of children born very preterm in Turku University Hospital, Finland, in 2001-2006.

Patients: A total of 170 children born very preterm were followed up until 11 years of age.

Main outcome measures: Motor and cognitive outcomes were evaluated using the Movement Assessment Battery for Children - Second Edition (Movement ABC-2) and the Wechsler Intelligence Scale for Children - Fourth Edition, respectively, and HRQoL using a 17-dimensional illustrated questionnaire (17D). The Touwen neurological examination was performed to exclude other neurological conditions affecting the motor outcome.

Results: Eighteen children born very preterm (17 boys) (11.3%) had DCD, defined as the Movement ABC-2 total test score $\leq 5^{th}$ percentile. A positive correlation between motor and cognitive outcome ($r=0.22$, $p=0.006$) was found. Children born very preterm with DCD had lower cognitive scores than those without DCD (full-scale intelligence quotient mean 76.8 vs. 91.6, $p=0.001$). Moreover, children born very preterm with DCD reported lower HRQoL than children born very preterm without motor impairment (17D mean 0.93 vs. 0.96, $p=0.03$). However, the HRQoL was higher in this group of children born very preterm compared to population based normative test results ($p<0.001$).

Conclusions: DCD was still common at 11 years of age in children born very preterm in 2000s . DCD associated with adverse cognitive development and lower self-experienced HRQoL. However, this group of children born very preterm reported better HRQoL in comparison with Finnish norms.

INTRODUCTION

The incidence of cerebral palsy (CP) has decreased among children born very preterm[1–6]. However, the rate of non-CP motor impairments such as developmental coordination disorder (DCD) has not decreased[7], and children born preterm are still at increased risk for cognitive impairment compared to term peers[8–11].

DCD is defined as motor problems interfering with academic achieving or activities of daily living which cannot be explained by medical, neurological or cognitive impairment[12]. The etiology of DCD is multifactorial, and neuroimaging studies have shown alterations in the brain development and functioning in children with DCD[13–16]. The prevalence of DCD has been shown to vary from 5 to 6% in school-aged children and from 8 to 51% in those born preterm[8,12,17–19]. DCD has been shown to co-occur with developmental disorders such as social, behavioral and attention problems, and learning difficulties[12,17,20–22]. Nevertheless, data of the relationship between DCD and cognitive development in early adolescence is limited[22].

Severe neurodevelopmental impairments such as CP, cognitive impairment, hearing and visual impairment have been reported to associate with poorer self-experienced health-related quality of life (HRQoL) in school aged children born preterm, while those without these morbidities have reported HRQoL equal to peers[23,24]. The effect of preterm birth on HRQoL seems to be most significant in younger years and seems to decrease over time[25]. The impact of motor impairments such as DCD on HRQoL is not well known. Dewey et. al. has found no differences on total HRQoL scores between adolescents with DCD and/or attention- deficit–hyperactivity disorder (ADHD), and typically developing adolescents. However, they found that adolescents with DCD and AHDH had lower HRQoL on the mood and emotions subscale, and school environment subscale. Their additional comparisons indicated that on both these subscales the adolescents with DCD and ADHD

had significantly lower scores than adolescents with DCD only. Karras et. al. has found that children with DCD reported significantly lower scores in four out of 10 HRQoL subscales: psychological well-being, moods and emotions, parent relations and home life, and school environment.[26,27]

The aims of this study were to evaluate the rate of DCD and to study the correlation between motor and cognitive development at 11 years of age in children born very preterm and/or very low birth weight in 2000s; and to study the effect of DCD on self-experienced HRQoL. We hypothesized that DCD is still common in children born very preterm and/or very low birth weight , and that poorer motor outcome correlates with adverse cognitive performance, and that DCD correlates with lower perceived HRQoL as compared to children born very preterm and/or very low birth weight without motor impairment.

METHODS

Participants

This prospective study is part of the PIPARI (**Pi**eni**pa**inoisten **ri**skilasten käyttäytyminen ja toimintakyky imeväisiästä kouluikään; The Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age) study of infants born very preterm[28,29]. The participants were born to Finnish- or Swedish-speaking families from January 2001 to December 2006 in Turku University Hospital, Finland, which is one of the five level III hospitals in Finland. From 2001 to 2003 the inclusion criteria were birth weight ≤1500g and prematurity (<37 gestational weeks). From 2004, the inclusion criteria were broadened to all infants born <32 weeks of gestational age irrespective of the birth weight. The exclusion criteria were severe congenital anomalies or diagnosed syndrome affecting cognitive development. The flow chart of the participants is shown in Figure 1. The Ethics Review Committee of the Hospital District of South-West Finland approved the study protocol in 2000 and in 2012. Written informed consent for this follow-up study were provided by parents and children. This study was done without patient and public involvement.

Motor outcome

The diagnosis of CP was confirmed based on the classification proposed by Himmelmann et al.[30] after a systematic clinical follow-up by two years of corrected age by an experienced child neurologist. The motor outcome of the children born very preterm without CP was evaluated at 11 years of age by one of the three physicians by using Movement Assessment Battery for Children – Second Edition (Movement ABC-2)[31,32]. The three physicians performing the motor and neurological assessments were PhD students of the PIPARI study group. The raw scores were converted into total standard scores and percentile scores according to the test manual, using the age band 3 (11 to 16 years) and the norms for 11-year-old children. A total test score >15th percentile

indicated no movement difficulty, >5th to 15th percentile indicated risk of movement difficulties, and ≤5th percentile denoted DCD[32]. Touwen neurological examination was used to confirm that there were no other neurological conditions such as muscle diseases affecting the motor development[32–34]. All the Movement ABC-2 assessments and Touwen neurological examinations were video recorded. In case of any hesitation regarding the assessments, the videos were reassessed by one experienced child neurologist (LH).

Cognitive outcome

The cognitive development of the children born very preterm at 11 years of age was assessed with the Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV), Finnish translation[35,36]. The assessments were performed either in Finnish or Swedish according to child's native language. Finnish assessments were performed by one of the two psychologists, who were PhD students of the PIPARI study group. Swedish speaking children were assessed by a native Swedish-speaking psychologist. General intelligence was measured with full-scale intelligence quotient (IQ), which consisted of the Verbal Comprehension Index, the Perceptual Reasoning Index, the Working Memory Index and the Processing Speed Index. The classification was based on the test manual[35,36]. The scores were classified as average if the full-scale IQ was ≥90, low average 80-89, and borderline 70-79. A full-scale IQ <70 was classified as severe cognitive impairment.

Health-related quality of life

The self-experienced HRQoL of children born very preterm at 11 years of age was evaluated using a generic self-assessment measure, a17-dimensional illustrated questionnaire (17D)[37]. It consisted of 17 multiple-choice questions of health and function. The domains were mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, school and hobbies, learning and memory, discomfort and symptoms, depression, distress, vitality, appearance, friends and concentration. Each domain

had a five-level tick box functioning scale alternating from a perfect level to a severe dysfunction. The children completed the questionnaire by themselves before the motor assessment except for one child who was not able to read and was interviewed by the physician before the assessment. The relative weights of each dimension were defined in the instrument's home page[38]. The overall HRQoL was calculated from the health state descriptive system using population-based preference or utility weights for 11-year-old healthy Finnish school children. The HRQoL score varied from zero (worst score, equals to death) to one (best score, equals complete health)[37].

Statistical Analysis

Difference in continuous background characteristics between study children born very preterm and the children who withdrew were studied using a two-sample t-test or a Wilcoxon two-sample test. For the categorical background characteristics, a chi-square test or Fisher's exact test were used. Correlations between the percentiles for the total scores of the Movement ABC-2 and full-scale IQ, and between the percentiles for the total scores of the Movement ABC-2 and WISC-IV indexes were calculated using Pearson correlations. Associations between DCD and background characteristics were studied using logistic regression analysis. Differences in the full-scale IQ and indexes between children born very preterm with and without DCD were studied using two-sample t-test. The associations between motor outcome (children born very preterm with and without DCD), cognitive outcome (full-scale IQ and indexes), and background characteristics (birth weight, gestational age, and mother's and father's education) were studied using the multiple linear regression model. The background characteristics were chosen a priori.

If up to three dimensions were missing from the 17D, multiple imputation was used to replace missing values with one value, as suggested by the instrument's home page (http://www.15d-instrument.net/15d/replacing-missing-data/) in order to calculate the 17D total score. If more than

three dimensions were missing, the questionnaire was not used in the analyses. Differences in the 17D scores between the groups of 1) children with and without DCD, 2) with and without CP and 3) with and without severe cognitive impairment were studied using Mann-Whitney U Test. The correlations between the Movement ABC-2 and the 17D as well as full-scale IQ and the 17D were studied using Spearman's correlation. The differences in 17D scores in study children born very preterm compared with Finnish population based normative results were studied using Mann-Whitney U Test. The statistical analyses were carried out using a 9.4 version of SAS Institute Inc. (Cary, NC, USA) for Windows. P-values of <0.05 were considered statistically significant.

RESULTS

A total of 170 children born very preterm were followed until 11 years of age. The follow-up rate was 77.6% (out of 219 participants). The background characteristics of study children and children who withdrew are shown in *Table 1*. The rate of CP did not differ between the study children and the children who withdrew (p=0.5). The mothers of the children who withdrew had lower educational level compared with mothers of the study children (53% vs 36% with ≤12 years of education, p=0.04). No other differences in background characteristics shown in *Table 1* were found between the study children and the children who withdrew.

Motor development

All the children born very preterm, including those with full-scale IQ <70, were able to follow the given instructions without any adaptations of test items and completed the Movement ABC-2. Accordingly, children born very preterm with full-scale IQ <70 were included in the analyses regarding DCD as suggested according to the recent European Academy of Childhood Disability recommendations[12]. There were nine (5.3%) children born very preterm with CP who were assessed at 11 years of age; they were excluded from the analyses regarding the Movement ABC-2.

Of all the 161 children born very preterm without CP, one child did not complete the Movement ABC-2. A total of 142 (88.8%) had a total test score >5th percentile. Of these children born very preterm, 12 (8.5%) had their score between 5th and 15th percentile in the Movement ABC-2 indicating a risk for motor problems. There were 18 children born very preterm (11.3%) with a total test score ≤5th percentile in the Movement ABC-2; these children were denoted having DCD after confirming with the Touwen neurological examination that they did not have such neurological findings or other neurological disorders which could explain their poor performance. Twelve of the children born very preterm with DCD were born extremely preterm (<28 gestational weeks) and/or with extremely low birth weight (≤1000g), representing 18.2% of all (n=66) extremely preterm and/or extremely low birth weight children. All but one of the children born very preterm with DCD were boys. Of the other background characteristics shown in *Table 1*, lower gestational age (p=0.04), bronchopulmonary dysplasia (p=0.04), sepsis (p=0.04), and major brain pathologies in the magnetic resonance imaging at term age (p=0.02) were associated with DCD.

Cognitive development

The mean value (SD, [min, max]) of the full-scale IQ for the whole very preterm study cohort (n=170) was 88.3 (17.0 [40.0, 131.0]). The mean value for the verbal comprehension was 90.3 (14.8, [46.0, 122.0]), for the perceptual reasoning 92.0 (17.1 [40.0, 122.0]), for the working memory 92.6 (16.3 [46.0, 133.0]) and for the processing speed 93.9 (17.4 [47.0, 153.0]). Of all the 161 children born very preterm without CP, 89 (55.3%) performed within the average range (full-scale IQ ≥90), 34 (21.1%) had low average performance (full-scale IQ ≥80-89), 25 (15.5%) had borderline cognitive development (full-scale IQ ≥70-79), and 13 (8.1%) had severe cognitive impairment (full-scale IQ <70). The mean values of the full-scale IQ and its four indexes are shown by categories of motor outcome in *Table 2*.

The Movement ABC-2 scores of children born very preterm without CP correlated positively with full-scale IQ (r=0.2, p=0.006), working memory index (r=0.3, p<0.001), processing speed index (r=0.2, p=0.03), and perceptual reasoning (r=0.2, p=0.03). The scatter plot of the full-scale IQ and the Movement ABC-2 is shown in *Figure 2*. Children born very preterm with DCD had lower full-scale IQ than children born very preterm without motor impairment (mean 76.8 vs. 91.6) (p<0.001). Similarly, children born very preterm with DCD scored lower than children born very preterm without motor impairment in all indexes as shown in *Table 2.* The results remained statistically significant after adjusting with birth weight, gestational age, and mother's and father's education.

Health-related quality of life

A total of 167 (98.2%) of the followed children born very preterm completed the 17D questionnaire. There were no statistically significant correlations between the Movement ABC-2 and the 17D (r=0.1, p=0.06) nor between the full-scale IQ and the 17D (r=0.07, p=0.4). However, children born very preterm with DCD had lower self-experienced HRQoL compared with children born very preterm without DCD (0.93 vs. 0.96, p=0.03). Children born very preterm with DCD showed more problems than children born very preterm without DCD on the dimensions considering vision (0.96 vs. 0.99, p=0.008), hearing (0.92 vs. 0.98, p=0.01), and speech (0.96 vs. 0.99, p=0.007). The HRQoL of children born very preterm with CP did not differ from the HRQoL of children born very preterm without CP (0.94 vs. 0.96, p=0.6), nor did the HRQoL in children born very preterm with severe cognitive impairment (full-scale IQ<70) from the children born very preterm without cognitive impairment (0.93 vs. 0.96, p=0.2). This cohort of children born very preterm reported better self-experienced HRQoL compared to Finnish population based normative results[37] (p<0.001). Children born very preterm showed less problems than the normative population on the dimensions considering sleeping (p=0.02), discomfort and symptoms (p<0.001), depression (p<0.001), vitality (p=0.02), appearance (p=0.03), friends (p=0.01), and concentration

(p=0.001).

DISCUSSION

This study showed that DCD is still common in 11-year-old children born very preterm in 2000s. Children born very preterm with DCD had worse cognitive development than children born very preterm without motor impairment. Moreover, children born very preterm with DCD reported lower HRQoL than children born very preterm without DCD. However, the HRQoL was higher in this study cohort of children born very preterm than in Finnish norm population.

The finding of a high rate of DCD in children born very preterm in early adolescence is parallel to the recently reported rising trend of non-CP motor impairments in children born extremely preterm at the age of 6.5 and 8 years[7,21]. The rate of DCD in children born extremely preterm of this PIPARI Study cohort was 18%, while two recent studies from Sweden and Australia have reported non-CP motor impairment rates of 26-37% in extremely preterm populations[7,21]. The Swedish study reported that the rate of non-CP motor impairment was 37% when they used a cut-off based on their control group, but if the normative cut-offs[32] had been used the rate would have been 12.5%. Some studies have reported the prevalence of non-CP motor impairment as being higher in boys[7,12], while others have shown no significant difference in the prevalence in boys and girls[21]. In the present study, all but one of the children with DCD were boys. However, the small number of children with DCD did not enable reliable statistical analysis regarding sex.

A positive correlation between motor outcome and cognitive development in children born very preterm was found even if the correlations were not strong in magnitude. Children born very preterm with DCD had lower mean scores in full-scale IQ and in all indexes compared with children born very preterm without motor impairment. The differences were clinically significant in magnitude, i.e. 15 points for full-scale IQ, 8 points for verbal comprehension, 9 for perceptual reasoning, 16 for working memory, and 13 for processing speed, all in favour of children without

DCD. This is in line with previous studies that have reported lower full-scale IQ and processing speed in children born very preterm with DCD at 5 years of age[22] and lower perceptual reasoning and processing speed in children born extremely preterm with DCD at 6.5 years of age[21]. However, as WISC-IV has some items in the processing speed and the perceptual reasoning index subtests requiring fine motor control (e.g. holding a pen, drawing in a small space, and manipulating blocks) it is possible that motor impairment may have an effect on child's performance in these subtests. According to our results, DCD might indicate also problems in cognitive development at 11 years of age in children born very preterm. Lower motor scores accumulated among boys born very preterm in the present study. Future research may expand current findings about possible mechanisms leading to vulnerability according to sex.

This study showed lower self-experienced HRQoL in children born very preterm with DCD compared to children born very preterm without motor impairment in early adolescence. The affected domains were vision, hearing, and speech. The absolute differences in HRQoL results between the groups were minor since the scoring system ranges from zero to one. Whether these statistically significant differences have clinical importance is not definite. A previous review using various instruments suggested difficulties in fine motor skills (and causing difficulty e.g. with brushing teeth, washing hair, dressing up and using knife and fork) and in social skills (causing e.g. loneliness and spending more time alone)[39]. Nevertheless, comparing different instruments should be treated with caution. Self-experienced HRQoL at 11 years of age was better in our study cohort of children born very preterm compared to the test normative at the same age in the Finnish population. This is an unexpected finding as children born very preterm have many impairments potentially lowering their HRQoL. The mothers of the children who withdrew from the study had lower educational level compared with mothers of the study children. This may have influenced the results and may offer one explanation why the study cohort of children born very preterm reported

their HRQoL better compared to the norms. However, we are not aware of differences in general health outcomes in 1990s and 2000s. In any case, good HRQoL in children born very preterm at 11 years of age is reassuring information for families with a preterm infant.

The strength of this study was a relatively high follow-up rate (78 %) from birth to 11 years of age. The examinations were performed with the latest version of the Movement ABC-2, and a thorough Touwen neurological examination was used to support the definition of DCD. A possible limitation was that the motor assessments were not done repeatedly as suggested in the latest European Academy of Childhood Disability recommendations[12]. However, these new guidelines were not available during the data collection. We also chose to use the strict cut-off of the 5th percentile to define clinically significant non-CP motor impairment. There was no possibility to compare the rate of DCD to peers born at term due to lack of a control group. To assess the cognitive development we used WISC-IV which is a validated and widely used tool in Finland and the national cut-offs are precise and up-to-date. Regarding the HRQoL results the Finnish normative of the same age population was available, although it was based on data collection before 1996. Although the sample size of the whole study group was satisfactory, the total number of children born very preterm with DCD and CP were small, which restricts the power of the statistical analysis concerning these groups and generalizability of the results.

CONCLUSIONS

This study supports previous findings that even though more preterm born infants survive without CP they still have an increased risk for DCD. Children born very preterm with DCD showed lower cognitive performance than children born very preterm without DCD. It is important to recognize motor problems early to provide interventions and support services needed and to provide cognitive assessments with a low threshold. The HRQoL of children born very preterm was to a large extent

good but did however differ between children born very preterm with DCD and those without motor impairment.

Acknowledgements:
For the collaboration regarding the 17D questionnaire: Marjo Apajasalo and Harri Sintonen.
The PIPARI Study Group: Mikael Ekblad, MD, PhD; Satu Ekblad, RN; Eeva Ekholm, MD, PhD; Annika Eurola, MD; Leena Haataja, MD, PhD; Mira Huhtala, MD, PhD; Jere Jaakkola, BM; Pentti Kero, MD, PhD; Riikka Korja, PhD; Katri Lahti, MD; Helena Lapinleimu, MD, PhD; Liisa Lehtonen, MD, PhD; Tuomo Lehtonen, MD; Marika Leppänen, MD, PhD; Annika Lind, PhD; Jaakko Matomäki, MSc; Jonna Maunu, MD, PhD; Petriina Munck PhD; Laura Määttänen, MD; Pekka Niemi, PhD; Anna Nyman, PhD; Pertti Palo, MD, PhD; Riitta Parkkola, MD, PhD; Liisi Ripatti, MD, PhD; Päivi Rautava, MD, PhD; Katriina Saarinen, Physiotherapist; Virva Saunavaara, PhD; Sirkku Setänen, MD, PhD; Matti Sillanpää, MD, PhD; Suvi Stolt, PhD; Sanna Sutinen, BM; Päivi Tuomikoski-Koiranen, RN; Timo Tuovinen, BA; Karoliina Uusitalo, MD; Anniina Väliaho, MA; Milla Ylijoki, MD, PhD.

Funding source: All phases of this study were supported by a grant from the Arvo and Lea Ylppö Foundation, the Emil Aaltonen Foundation, the Finnish Medical Foundation, the Finnish Cultural Foundation, the South-Western Finnish Foundation of Neonatal Research, the Turku University Research Foundation, and the Yrjö Jahnsson Foundation.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Potential Conflicts of Interest: The authors have no conflicts of interest to disclose.

Clinical Trial Registration: The PIPARI study has not been registered as clinical trial since it is not an intervention study.

References

1. Platt MJ, Cans C, Johnson A, et al. Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study. *Lancet*. 2007;369(9555):43-50. doi:10.1016/S0140-6736(07)60030-0
2. Groenendaal F, Termote J, Van Der Heide-Jalving M, Van Haastert I, De Vries L. Complications affecting preterm neonates from 1991 to 2006: What have we gained? *Acta Paediatr Int J Paediatr*. 2010;99(3):354-358. doi:10.1111/j.1651-2227.2009.01648.x
3. Sellier E, Platt MJ, Andersen GL, et al. Decreasing prevalence in cerebral palsy: A multi-site European population-based study, 1980 to 2003. *Dev Med Child Neurol*. 2016;58(1):85-92. doi:10.1111/dmcn.12865
4. Fawke J. Neurological outcomes following preterm birth. *Semin Fetal Neonatal Med*. 2007;12(5):374-382. doi:10.1016/j.siny.2007.06.002
5. Guerrot A-M, Chadie A, Torre S, et al. Compared outcomes of very preterm infants born in 2000 and 2005. *Acta Paediatr*. 2012;101(7):731-735. doi:10.1111/j.1651-2227.2012.02678.x
6. Holsti A, Adamsson M, Serenius F, H??ggl??f B, Farooqi A. Two-thirds of adolescents who received active perinatal care after extremely preterm birth had mild or no disabilities. *Acta Paediatr*. 2016;105(11):1288-1297. doi:10.1111/apa.13499
7. Spittle AJ, Cameron K, Doyle LW, Cheong JL. Motor impairment trends in extremely preterm children: 1991-2005. *Pediatrics*. 2018. doi:10.1542/peds.2017-3410
8. Pascal A, Govaert P, Oostra A, Naulaers G, Ortibus E, Van den Broeck 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. doi:10.1111/dmcn.13675
9. 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;352(1):9-19. doi:10.1056/NEJMoa041367
10. Anderson PJ. Neuropsychological outcomes of children born very preterm. *Semin Fetal Neonatal Med*. 2014;19(2):90-96. doi:10.1016/j.siny.2013.11.012
11. Nyman A, Korhonen T, Munck P, Parkkola R, Lehtonen L, Haataja L. Factors affecting the cognitive profile of 11-year-old children born very preterm. *Pediatr Res*. 2017;82(2):324-332. doi:10.1038/pr.2017.64
12. Blank R, Barnett AL, Cairney J, et al. International clinical practice recommendations on the definition, diagnosis, assessment, intervention, and psychosocial aspects of developmental coordination disorder. *Dev Med Child Neurol*. 2019. doi:10.1111/dmcn.14132
13. Brown-Lum M, Zwicker JG. Brain Imaging Increases Our Understanding of Developmental Coordination Disorder: a Review of Literature and Future Directions. *Curr Dev Disord Reports*. 2015;2(2):131-140. doi:10.1007/s40474-015-0046-6
14. Biotteau M, Chaix Y, Blais M, Tallet J, Péran P, Albaret JM. Neural signature of dcd: A critical review of mri neuroimaging studies. *Front Neurol*. 2016. doi:10.3389/fneur.2016.00227
15. Lahti K, Saunavaara V, Munck P, et al. Diffusion tensor imaging is associated with motor outcomes of very preterm born children at 11 years of age. *Acta Paediatr Int J Paediatr*. 2019;(January):1-8. doi:10.1111/apa.15004
16. Dewey D, Thompson DK, Kelly CE, et al. Very preterm children at risk for developmental coordination disorder have brain alterations in motor areas. *Acta Paediatr Int J Paediatr*. 2019;108(9):1649-1660. doi:10.1111/apa.14786
17. Zwicker JG, Missiuna C, Harris SR, Boyd LA. Developmental coordination disorder: A review and update. *Eur J Paediatr Neurol*. 2012;16(6):573-581. doi:10.1016/j.ejpn.2012.05.005

18. Ferrari F, Gallo C, Pugliese M, et al. Preterm birth and developmental problems in the preschool age. Part I: Minor motor problems. *J Matern Neonatal Med*. 2012. doi:10.3109/14767058.2012.696164
19. Setänen S, Lehtonen L, Parkkola R, et al. The motor profile of preterm infants at 11 y of age. *Pediatr Res*. 2016;80(3). doi:10.1038/pr.2016.90
20. Harrowell I, Hollén L, Lingam R, Emond A. The impact of developmental coordination disorder on educational achievement in secondary school. *Res Dev Disabil*. 2018. doi:10.1016/j.ridd.2017.10.014
21. 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;172(8):765-774. doi:10.1001/jamapediatrics.2018.1394
22. Van Hus JW, Potharst ES, Jeukens-Visser M, Kok JH, Van Wassenaer-Leemhuis AG. Motor impairment in very preterm-born children: Links with other developmental deficits at 5 years of age. *Dev Med Child Neurol*. 2014;56(6):587-594. doi:10.1111/dmcn.12295
23. Huhtala M, Korja R, Rautava L, et al. Health-related quality of life in very low birth weight children at nearly eight years of age. *Acta Paediatr*. 2016;105(1):53-59. doi:10.1111/apa.13241
24. Natalucci G, Bucher HU, Von Rhein M, Borradori Tolsa C, Latal B, Adams M. Population based report on health related quality of life in adolescents born very preterm. *Early Hum Dev*. 2017;104:7-12. doi:10.1016/j.earlhumdev.2016.11.002
25. Zwicker JG, Harris SR. Quality of life of formerly preterm and very low birth weight infants from preschool age to adulthood: a systematic review. *Pediatrics*. 2008;121(2):e366-76. doi:10.1542/peds.2007-0169
26. Karras HC, Morin DN, Gill K, Izadi-Najafabadi S, Zwicker JG. Health-related quality of life of children with Developmental Coordination Disorder. *Res Dev Disabil*. 2018;(August 2017):1-11. doi:10.1016/j.ridd.2018.05.012
27. Dewey D, Volkovinskaia A. Health-related quality of life and peer relationships in adolescents with developmental coordination disorder and attention-deficit-hyperactivity disorder. *Dev Med Child Neurol*. 2018:711-718. doi:10.1111/dmcn.13753
28. Pipari web page. https://sites.utu.fi/pipari/en/.
29. Setänen S, Lehtonen L, Lapinleimu H, Haataja L, on behalf of the PIPARI Study group. Lessons learnt about the long-term neurodevelopment in very preterm born children in the PIPARI Study. *Lääketieteellinen Aikakausk Duodecim*. 2018;134(2):118-125. https://www.duodecimlehti.fi/duo14135#duo-comments-start.
30. Himmelmann K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995-1998. *Acta Paediatr Int J Paediatr*. 2005. doi:10.1080/08035250410023313
31. Henderson S, Sugden D. The movement assessment battery for children. *Phys Ther*. 1992;23:286-294. doi:10.1111/ppe.12025
32. Henderson S, Sugden D, Barnett A. *Movement Assessment Battery for Children (Examiner's Manual)*. London: Pearson Assessment; 2007.
33. Touwen BCL. *The Examination of the Child with Minor Neurological Dysfunction*.; 1979.
34. Hadders-Algra M. *The Neurological Examination of the Child With Minor Neurological Dysfunction, 3rd Edn.* London: Mac Keith Press; 2010.
35. Wechsler D. *Wechsler Intelligence Scale for Children -IV. Käsikirja I. Esitys Ja - Pisteytysohjeet (Handbook I. Administration and Scoring)*. Jyväskylä Psykologien Kustannus; 2011.
36. Wechsler D. *Wechsler Intelligence Scale for Children -IV. Käsikirja II. Teoriatausta, Standardointi Ja Tulkinta (Handbook II. Theoretical Background, Standardization and*

Interpretation). Jyväskylä Psykologien Kustannus; 2011.
37. Apajasalo M, Rautonen J, Holmberg C, et al. Quality of life in pre-adolescence: A 17-dimensional health-related measure (17D). *Qual Life Res*. 1996;5(6):532-538. doi:10.1007/BF00439227
38. Apajasalo M, Rautonen J, Holmberg C, et al. 17D. http://www.15d-instrument.net/16d-and-17d/17d/.
39. Zwicker JG, Harris SR, Klassen AF. Quality of life domains affected in children with developmental coordination disorder: A systematic review. *Child Care Health Dev*. 2013. doi:10.1111/j.1365-2214.2012.01379.x

Table 1. Background characteristics of the 11-year-old children (n=170) born at very low gestational age (<32 weeks) or with a very low birth weight (≤1500g).

Characteristics	Study children, n=170	Children who withdrew, n=49	P-value
Gestational age, mean (SD) [min, max], wk	29.1 (2.7) [23.0, 35.9]	29.0 (2.7) [23.7, 34.1]	0.9
Birth weight, mean (SD) [min, max], g	1134.4 (315.3) [400.0, 2120.0]	1184.6 (374.5) [565.0, 1970.0]	0.3
Small for gestational age (<-2 SD), n (%)	56 (32.9)	11 (22.5)	0.2
Male, n (%)	94 (55.3)	30 (61.2)	0.5
Caesarean section, n (%)	101 (59.4)	32 (65.3)	0.5
Bronchopulmonary dysplasia, n (%)	22 (12.9)	7 (14.3)	0.8
Operated necrotizing enterocolitis, n (%)	7 (4.2)	3/48 (6.3)	0.7
Sepsis, n (%)	30 (17.7)	7 (14.3)	0.6
Laser-treated retinopathy of prematurity, n (%)	4 (2.4)	3/47 (6.4)	0.2
Brain magnetic resonance imaging at term age			0.9
Normal findings, n (%)	96/165 (58.2)	29/48 (60.4)	
Minor pathologies, n (%)	27/165 (16.4)	7/48 (14.6)	
Major pathologies, n (%)	42/165 (25.5)	12/48 (25.0)	
Mother's education,			0.04
≤12 years, n (%)	61/168 (36.3)	24/45 (53.3)	
>12 years, n (%)	107/168 (63.7)	21/45 (46.7)	
Father's education,			0.4
≤12 years, n (%)	110/166 (66.3)	32/44 (72.7)	
>12 years, n (%)	56/166 (33.7)	12/44 (27.3)	

*The specific MRI protocol and details about the classification of the findings have been previously described by Setänen et al. (Setänen S, Haataja L, Parkkola R, Lind A, Lehtonen L. Predictive value of neonatal brain MRI on the neurodevelopmental outcome of preterm infants by 5 years of age. *Acta Paediatr*. 2013. doi:10.1111/apa.12191)

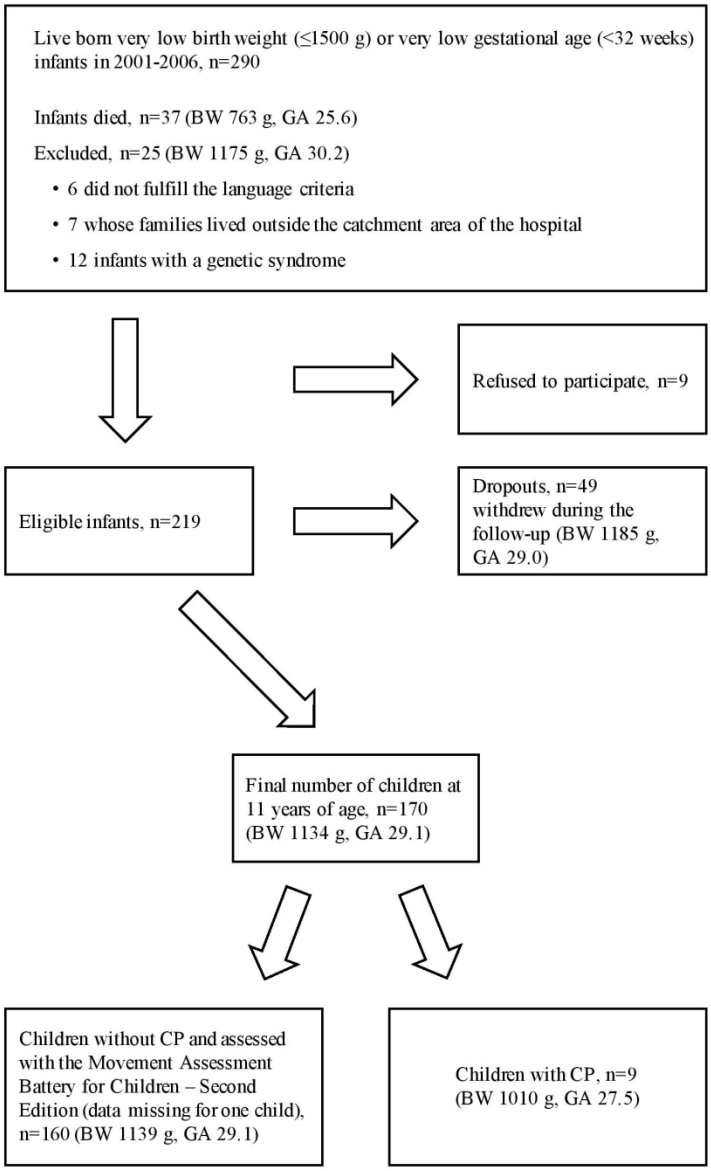
Table 2. Cognitive outcome shown in 11-year-old children born very preterm with cerebral palsy (CP) and according to the performance in Movement Assessment Battery for Children in children without CP. The mean values (SD), [minimum, maximum] of full-scale intelligence quotient and its four indexes are shown. The outcomes are compared between children with developmental coordination disorder (DCD) and children without motor impairment (two-sample t-test).

	CP, n=9	DCD, ≤5th percentile, n=18	Children without motor impairment, >5 percentile, n=142	P-value
Full-scale intelligence quotient	62.4 (22.8) [40.0, 97.0]	76.8 (18.2) [40.0, 100.0]	91.6 (14.3) [52.0, 131.0]	<0.001*
Verbal comprehension	75.1 (21.1) [46.0, 98.0]	83.8 (16.3) [46.0, 108.0]	92.1 (13.4) [60.0, 122.0]	0.02*
Perceptual reasoning	64.8 (23.1) [40.0, 100.0]	85.7 (17.9) [51.0, 109.0]	94.8 (14.6) [62.0, 122.0]	0.02*
Working memory	77.0 (20.5) [46.0, 109.0]	79.2 (13.9) [46.0, 97.0]	95.4 (15.0) [55.0, 133.0]	<0.001*
Processing speed	72.4 (21.4) [47.0, 106.0]	83.3 (19.4) [47.0, 118.0]	96.5 (15.5) [56.0, 153.0]	0.001*

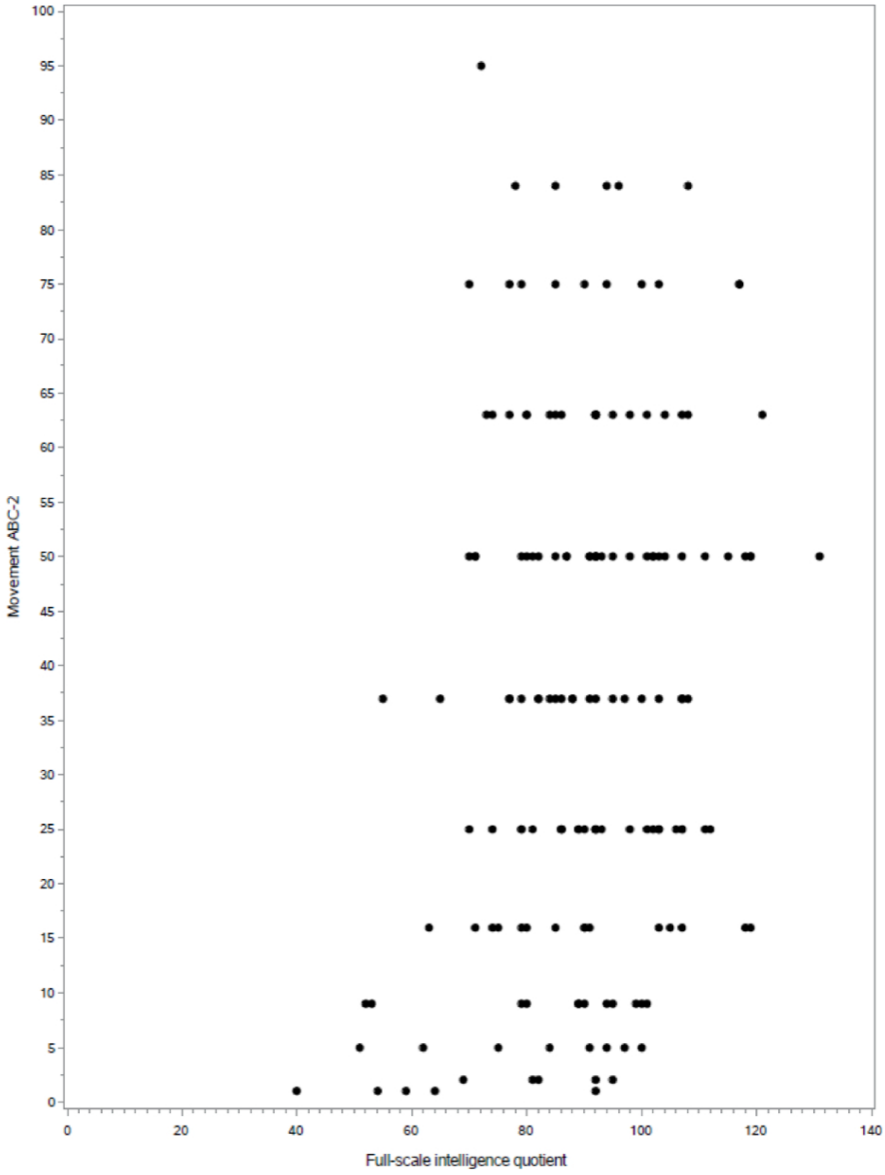
*The results remained statistically significant after adjusting with birth weight, gestational age, and mother's and father's education.

Figure 1.
Flow chart of the participants, mean of gestational ages (GA) in weeks and birth weights (BW).

Figure 2. The scatter plot of the full-scale intelligence quotient and percentiles for the total scores of the Movement Assessment Battery for Children – Second Edition (Movement ABC-2) at 11 years of age in children born very low birth weight (≤1500g) or very low gestational age (<32 weeks).



143x213mm (300 x 300 DPI)


Movement ABC-2
Full-scale intelligence quotient
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
0
20
40
60
80
100
120
140