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Motor difficulties among children born extremely preterm : risk factors and consequences for quality of life

Adrien Aubert

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Université Paris Cité

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Thèse préparée dans le cadre du réseau doctoral en santé publique animé par l'EHESP

Motor difficulties among children born extremely preterm: risk factors and consequences for quality of life

Par Adrien AUBERT

THÈSE DE DOCTORAT – Spécialité Épidémiologie

Dirigée par Jennifer ZEITLIN

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Abstract in English

Title: Motor difficulties among children born extremely preterm: risk factors and consequences for quality of life.

Children born extremely preterm (EPT, <28 weeks of gestation) face higher risks of long-term developmental motor problems than their term-born peers, including cerebral palsy (CP) and non-CP movement difficulties (MD). Multiple questions remain unanswered about the motor consequences of EPT birth. For instance, the prevalence of non-CP MD is not well described, as it varies greatly between studies, and results on associated risk factors have been inconsistent. Further, despite the proven effectiveness of interventions to improve motor performance in children born EPT with developmental motor problems, research on their healthcare use is sparse. Lastly, impaired motor function can limit daily activities, schooling and social relationships, however, the consequences of CP and non-CP MD on children's health-related quality of life (HRQoL) have not been investigated.

This doctoral work aimed to i) estimate the prevalence of CP and non-CP MD among children born EPT; ii) explore associated sociodemographic, perinatal and neonatal risk factors; iii) investigate motor-related health care (MRHC) services used by EPT children with motor problems; and iv) measure their impact on the child's HRQoL.

We used data from a multi-country population-based cohort of EPT births in 2011-2012 in 19 regions in 11 European countries with perinatal and neonatal data abstracted from medical records and follow-up using parental questionnaires when the children were age five (N=1,021). We used the Movement Assessment Battery for Children – 2nd Edition to identify children at risk for MD and with significant MD, defined as scores $\leq 15^{\text{th}}$ and $\leq 5^{\text{th}}$ percentiles, respectively. Parents reported on CP diagnosis, the use of MRHC services over the past year and about their children's HRQoL.

We found that 11.1% of children had a CP diagnosis, while 23.2% of children without CP were at-risk for MD and 31.7% had significant MD. We identified multiple clinical risk factors that could be used to identify at-risk children for follow-up and early intervention services. We also showed associations with sociodemographic factors, with children from more disadvantaged families experiencing higher risks. Differences in prevalence of MD between countries also persisted after adjustment for population characteristics. Some risk factors were associated with both CP and non-CP MD, but risk factor profiles remained distinct, with medical factors at birth affecting CP risk more strongly. While around 90% of children with CP were receiving MRHC services, this was not the case for children with non-CP MD. Only 42.8%

of children with significant MD were receiving MRHC services with variation between countries ranging from 23.3% to 66.7%. Children with MD and other developmental difficulties were more likely to receive MRHC services. In comparison to EPT children without MD, HRQoL was lowest for children with CP, followed by those with significant MD and at risk for MD. For children with CP, HRQoL decreases were observed at all quantiles of the outcome, whereas for children with non-CP MD, decreases were non-significant at quantile 90 and more pronounced at the lower quantiles.

These results underscore the importance of MD as a consequence of EPT birth. Given its high prevalence, MD should be systematically integrated into follow-up. Our results also suggest that better guidelines and training are needed, taking into consideration children's social circumstances, to ensure that these difficulties are detected and that effective interventions are provided. Further research is needed on the mitigating or protective individual, familial or broader environmental factors that may preserve HRQoL, which may also contribute to differences observed between the countries in our European cohort.

Keywords: extremely preterm birth, motor difficulties, motor impairment, cerebral palsy, developmental coordination disorder, health care service use, follow-up, quality of life, birth cohort, Europe

Abstract in French

Titre : Difficultés motrices des enfants nés très grands prématurés : facteurs de risque et conséquences sur la qualité de vie.

Les enfants nés très grands prématurés (TGP, <28 semaines d'âge gestationnel), sont plus à risque d'avoir des problèmes du développement moteur (PDM) que ceux nés à terme, avec notamment des paralysies cérébrales (PC) et d'autres troubles moteurs (TM) plus fréquents. Cependant, de nombreuses interrogations persistent concernant les conséquences motrices de la naissance TGP. Par exemple, les estimations de la prévalence des TM ainsi que les facteurs de risque associés varient considérablement entre les études. Bien que les interventions visant à améliorer les performances motrices des enfants avec un PDM soient bénéfiques, les informations sur l'utilisation des services de santé (USS) reçus par ces enfants sont rares. Enfin, l'altération des fonctions motrices peut limiter les activités quotidiennes et scolaires ainsi que les relations sociales, or, les conséquences des PDM sur la qualité de vie liée à la santé (QdVLS) des enfants ne sont pas bien décrites.

Ce travail doctoral visait à i) estimer la prévalence de la PC et des TM chez les enfants nés TGP, ii) explorer les facteurs de risque sociodémographiques, périnataux et néonataux associés, iii) étudier l'USS des enfants nés TGP et présentant des PDM, et iv) mesurer l'impact des PDM sur la QdVLS de l'enfant.

Nos travaux ont utilisé les données d'une cohorte de naissances TGP en population en 2011-2012 dans 19 régions de 11 pays d'Europe, avec les données périnatales et néonatales provenant des dossiers médicaux et un suivi par questionnaire parental à l'âge de cinq ans (N=1021). Le *Movement Assessment Battery for Children – 2nd Edition* a été utilisé pour identifier les enfants à risque de TM (score $\leq 15^{\text{e}}$ percentile) ou ayant des TM manifestes ($\leq 5^{\text{e}}$ percentile). À cinq ans, les parents rapportaient également un éventuel diagnostic clinique de PC, l'USS de l'année écoulée, et la QdVLS de leur enfant.

Nous avons constaté que 11,1 % des enfants avaient une PC, alors que 23,2 % des enfants sans PC étaient à risque de TM et 31,7 % avaient des TM manifestes. De multiples facteurs de risque cliniques pouvant servir à la détection des enfants à risque qui pourrait bénéficier d'interventions précoces ont été identifiés. Nous avons également montré des associations avec des facteurs sociodémographiques, avec les enfants des familles défavorisées plus à risque de PDM. Les différences de prévalence des TM entre les pays persistaient après ajustement sur les caractéristiques de la population. Certains facteurs étaient associés à la fois aux risques de PC et TM, mais les profils restaient différents avec la

PC plus fortement associée aux facteurs médicaux. Près de 90 % des enfants avec un diagnostic de PC étaient suivis par des services de santé en lien à la motricité à l'âge de cinq ans en comparaison avec seulement 42,8 % des enfants ayant des TM manifestes, avec une variabilité entre les pays de 23,3 % à 66,7 %. Les enfants avec des TM et présentant d'autres difficultés de développement avaient plus de chance d'être suivis. Par rapport aux enfants sans TM, la QdVLS était plus faible pour les enfants avec une PC, suivis par ceux ayant des TM manifestes et à risque de TM. Pour l'ensemble des enfants ayant une PC, une réduction significative de la QdVLS était observée, contrairement aux enfants présentant des TM pour lesquels une partie d'entre eux avait une QdVLS identique à celle des enfants sans TM.

Ces résultats montrent l'importance des PDM comme conséquence de la naissance TGP. Au regard de sa forte prévalence, les TM doivent être systématiquement intégrés aux suivis. Nos résultats suggèrent qu'une amélioration des recommandations et de la formation est nécessaire, incluant la prise en compte du contexte social de l'enfant, pour permettre à ces difficultés d'être détectées et prises en charge plus efficacement. Des recherches supplémentaires sont nécessaires sur les facteurs atténuants ou protecteurs individuels, familiaux ou environnementaux qui préservent la QdVLS de certains enfants.

Mots clés : très grande prématurité, difficultés motrices, déficience motrice, paralysie cérébrale, trouble développemental de la coordination, utilisation des services de santé, suivi, qualité de vie, cohorte de naissance, Europe

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Other original articles published on the EPICE-SHIPS cohort

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- Costa R, **Aubert AM**, Seppänen AV, Ådén U, Sarrechia I, Zemlin M, Cuttini M, Männamaa M, Pierrat V, van Heijst AF, Barros H, Zeitlin J, Johnson S, and the SHIPS Research group. Prediction of movement difficulties at 5 years from parent report at 2 years in children born extremely preterm. *Developmental Medicine & Child Neurology*. 2023;Feb22. Access: <https://doi.org/10.1111/dmcn.15518>
- Kim SW, Andronis L, Seppänen AV, **Aubert AM**, Barros H, Draper ES, Sentenac M, Zeitlin J, Petrou S, on behalf of the SHIPS Research Group. Health-related quality of life of children born very preterm: a multinational European cohort study. *Qual Life Res*. 2022;Aug17. DOI: [10.1007/s11136-022-03217-9](https://doi.org/10.1007/s11136-022-03217-9)
- Seppänen AV, Draper ES, Petrou S, Barros H, **Aubert AM**, Andronis L, Kim SW, Maier RF, Pedersen P, Gadzinowski J, Lebeer J, Ådén U, Toome L, van Heijst AF, Cuttini M, Zeitlin J, on behalf of the SHIPS Research Group. High healthcare use at age five in a European cohort of children born very preterm. *J Pediatr*. 2021;Dec15. DOI: [10.1016/j.jpeds.2021.12.006](https://doi.org/10.1016/j.jpeds.2021.12.006)
- Kim SW, Andronis L, Seppänen AV, **Aubert AM**, Zeitlin J, Barros H, Draper ES, Petrou S, on behalf of the SHIPS Research Group. Economic costs at age five associated with very preterm birth: multinational European cohort study. *Pediatr Res*. 2021;Nov12. DOI: [10.1038/s41390-021-01769-z](https://doi.org/10.1038/s41390-021-01769-z)
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- Seppänen AV, Sauvegrain P, Draper ES, Toome L, El Rafei R, Petrou S, Barros H, Zimmermann LJI, Cuttini M, Zeitlin J, and the **SHIPS Research Group***. Parent's ratings of post-discharge healthcare for their children born very preterm and their suggestions for improvement: a European cohort study. *Pediatr Res*. 2021 Mar;89(4):1004-1012. DOI: [10.1038/s41390-020-01120-y](https://doi.org/10.1038/s41390-020-01120-y)

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Supplemental material

NB: The same labelling as in the published articles.

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List of abbreviations

ADHD, Attention deficit hyperactivity disorder
β, Beta
BPD, Bronchopulmonary dysplasia
BW, Birth weight
CCTIRS, French Advisory Committee on Use of Health Data in Medical Research
CI, Confidence interval
CLAD, Censored least absolute deviations (model)
CNIL, French National Commission for Data Protection and Liberties
CP, Cerebral palsy
cPVL, Cystic periventricular leukomalacia
DCD, Developmental coordination disorder
DSM, Diagnostic and Statistical Manual of Mental Disorders
EFCNI, European Foundation of the Care of Newborn Infants
ELBW, Extremely low birth weight
EPICE, Effective Perinatal Intensive Care in Europe
EPT, Extremely preterm
GA, Gestational age
GMFCS, Gross motor function classification system
HELLP, Hemolysis, Elevated Liver enzyme, Low Platelets (syndrome)
HRQoL, Health-related quality of life
ICD, International Classification of Diseases
ISCED, International Standard Classification of Education
IPW, Inverse probability weighting
IQ, Intelligence quotient
IVH, Intraventricular haemorrhage
MABC, Movement Assessment Battery for Children (1st Edition)
MABC-2, Movement Assessment Battery for Children (2nd Edition)
MD, Movement difficulties
MRI, Magnetic resonance imaging
NEC, Necrotising enterocolitis
NDI, Neurodevelopmental impairment
PedsQL, Pediatric Quality of Life Inventory™
PROM, Premature rupture of membranes
QoL, Quality of life
RCT, Randomised control trial
ROP, Retinopathy of prematurity
SD, Standard deviation
SGA, Small for gestational age
SHIPS, Screening to Improve Health in Very Preterm Infants in Europe
VLBW, Very low birth weight
VPT, Very preterm
WHO, World Health Organization
WMA, White matter abnormalities
WPSSI, Wechsler Preschool and Primary Scale of Intelligence

1.1. General context

More than one in 10 infants are born prematurely worldwide, accounting for around 15 million births per year (Blencowe et al., 2013; Chawanpaiboon et al., 2019). Preterm birth is defined by the World Health Organization (WHO) as birth before 37 weeks' gestational age (GA) (World Health Organization, 2018). The vast majority of preterm infants are born between 32 and 37 weeks' GA (Blencowe et al., 2013), defined as moderate to late preterm, while around 1.5-2% of all infants (15-20% of all preterm births) are born very preterm (VPT; <32 weeks' GA) and 0.5-1% are born extremely preterm (EPT; <28 weeks' GA) (Blencowe et al., 2012).

While all children born preterm face higher risks of adverse short and long-term health and developmental outcomes than children born at term, those born at the lowest gestational ages are most vulnerable and disproportionately contribute to the burden of perinatal mortality and morbidity. In Europe, more than half of all neonatal deaths (deaths between 0 and 27 days after live birth) occur among the <1% of all babies who are born EPT (Euro-Peristat, 2022). And while advances in obstetric and neonatal care have led to markedly improved survival after EPT birth over past decades (Ancel et al., 2015; Goldenberg et al., 2008; Rogers and Hintz, 2016; Saigal and Doyle, 2008; Stoll et al., 2015; Tucker and McGuire, 2004), survivors face substantially higher risks of multiple long-term developmental problems than children born at later gestations, including motor, sensorial, cognitive and behavioural impairments (Allotey et al., 2018; Doyle et al., 2021; Moreira et al., 2014).

Impairments of motor function are among the most common consequences of EPT birth, ranging from highly disabling disorders to a small reduction of motor skills and comprise cerebral palsy (CP), developmental coordination disorder (DCD) and other movement difficulties (MD) (Adams-Chapman et al., 2018; Baron and Rey-Casserly, 2010; Bolk et al., 2018; Hafström et al., 2018; de Kieviet et al., 2009; Linsell et al., 2016; Spittle et al., 2018; Williams et al., 2010). CP is a well-defined neurodevelopmental disorder with a specific aetiology (Himmelman et al., 2006; Rosenbaum et al., 2007; Shapiro, 2004), that describes “a group of permanent disorders of the development of movement and posture, causing activity limitation, which are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain” (Rosenbaum et al., 2007, p5). In contrast, non-CP developmental motor problems, or “motor deficits in coordination, balance, gross and fine

motor control, and visual motor integration” (Spittle and Orton, 2014), are less consensually defined and different terms are used, often interchangeably and incorrectly, to delineate this range of problems (Gueze et al., 2001; Spittle and Orton, 2014); e.g., DCD, motor disorders, motor impairments, motor-skill impairments, etc. In this thesis work, we use the term developmental motor problems (or motor problems) to refer to both CP and non-CP motor impairments, while we use movement difficulties (MD) for children without CP based on the terminology employed by the Movement Assessment Battery for Children – 2nd Edition’s (MABC-2) manual (Henderson et al., 2007).

CP has a prevalence of around 10% among EPT children in contemporary studies or more than 100-times more often than their term-born peers (Adams-Chapman et al., 2018; Hafström et al., 2018; Himpens et al., 2008), whereas the prevalence of non-CP motor problems is less well established with wide variations between studies from 8% (Setänen et al., 2016) to more than 40% (Bolk et al., 2018; Bos et al., 2013; Spittle et al., 2021; Williams et al., 2010). These developmental motor problems reduce the child’s opportunities to develop in multiple areas and have been associated with impaired cognitive development, school performance, social integration, and functioning in adulthood (Allotey et al., 2018; Blank et al., 2019; Husby et al., 2016; de Kieviet et al., 2009; Moreira et al., 2014; Oudgenoeg-Paz et al., 2017; Spittle et al., 2021; Van Hus et al., 2014).

Despite a growing evidence base on the motor consequences of EPT birth, our understanding remains limited, particularly among children without CP for whom we have fewer studies. For instance, existing research provides inconclusive results on early life risk factors for non-CP MD, with consistent associations only for male sex and preterm birth (van Hoorn et al., 2021; Linsell et al., 2016). A better understanding, of the range of developmental motor problems experienced by children born EPT and the clinical and social characteristics associated with these risks is essential to implement appropriate early intervention and follow-up by clinicians and caregivers (McIntyre et al., 2011; Spittle and Orton, 2014). Early interventions have been shown to be effective (Smits-Engelsman et al., 2013; Spittle et al., 2015), but information on healthcare service use among EPT children with motor problems is sparse. Lastly, the consequences of these developmental motor problems on children’s lives and well-being are not well described (Vederhus et al., 2010; Zwicker et al., 2013).

1.2. Aim and objectives

The aim of this doctoral work is to generate new knowledge on developmental motor problems experienced by children born EPT at five years of age, including risk factors, management and consequences for quality of life. We base our research on data from the Screening to Improve Health in Very Preterm Infants in Europe (SHIPS) study which followed-up the Effective Perinatal Intensive Care in Europe (EPICE) population-based, prospective cohort of children born before 32 weeks' GA, in 2011-2012, in 19 regions in 11 European countries (Zeitlin et al., 2020a). At five years of age (in 2016-2017), only children born before 28 weeks' GA were invited for a clinical assessment evaluating neurocognitive and motor functioning. Thus, a sub-sample of this cohort, restricted to children born EPT was used to answer the four specific objectives of this thesis:

- i) Estimate the prevalence of motor problems among those children;
- ii) Explore the sociodemographic, perinatal and neonatal risk factors associated with these motor problems;
- iii) Investigate healthcare service use by EPT children with motor problems;
- iv) Measure the impact of motor problems on children's lives and well-being.

To address these four objectives, we performed four different studies. The first study (*chapter 4*) estimated the prevalence of non-CP MD and identified their associated sociodemographic, perinatal and neonatal risk factors. These results were published in *Pediatrics* in a manuscript entitled *Movement difficulties at age five among extremely preterm infants* (Aubert et al., 2022).

The second study (*chapter 5*) compared sociodemographic, perinatal and neonatal risk factors for CP and non-CP MD. These results were reported in an article entitled *Risk factors for cerebral palsy and movement difficulties in 5-year-old children born extremely preterm* published in *Pediatric Research* (Aubert et al., 2023).

In parallel with these two studies, we investigated healthcare service use to determine the proportion of five-year-old children born EPT with MD or CP receiving motor-related health care (MRHC) services; and describing the factors associated with receiving MRHC services (*chapter 6*). These results were reported in a manuscript entitled *Motor-related health care for 5-year-old children born extremely preterm with movement impairments* and published in *Developmental Medicine and Child Neurology* (Costa et al., 2022). I was second author for this work in collaboration with Raquel Costa, a developmental psychologist and post-doctoral researcher from the Institute for Public Health of the University of Porto.

The last study (*chapter 7*) measured the association between CP and non-CP MD and children's health related quality of life (HRQoL). This manuscript, entitled *Movement difficulties and health-related quality of life among five-year-old children born extremely preterm in a European multi-country cohort* has been submitted for publication and is under review.

These studies were carried out in collaboration with the SHIPS research group including researchers and clinicians from 13 collaborating institutions in 11 European countries, including one principal investigator and coordinators, clinicians and researchers in each country, a health economics team, and a parental organisation with the European Foundation of the Care of Newborn Infants (EFCNI). The EPICE and SHIPS projects were coordinated by the EPOPé team (Principal investigator: Jennifer Zeitlin) at the French National Institute of Health and Medical Research (Inserm, CRESS, UMR 1153).

This thesis work benefited from collaboration within a SHIPS working group on the developmental follow-up of the cohort which included Ulrika Ådén, professor of neonatology at Karolinska Institute (Sweden), Raquel Costa, developmental psychologist and post-doctoral researcher at the University of Porto (Portugal), Samantha Johnson, developmental psychologist and professor of child development at the University of Leicester (the United Kingdom) and Véronique Pierrat, neonatologist with expertise in the development of children born EPT, EPOPé team (France). Their expertise and contribution were invaluable for decisions regarding data cleaning and validation and for the interpretation of results.

Chapter 2 – State of the art

This chapter provides an overview of extreme prematurity and its associated short and long-term morbidities (2.1), followed by a more in-depth presentation of developmental motor problems (2.2), the measure of the consequences of motor problems on children's day-to-day life (2.3), and motor related healthcare interventions and support for the child (2.4).

2.1. Extreme prematurity as a high-risk condition

2.1.1. Survival after extremely preterm birth and changes over time

Extreme preterm birth is defined by the WHO as birth <28 weeks' GA (World Health Organization, 2018), but some studies use other thresholds (e.g., <27 weeks' GA) (Sentenac et al., 2022); and early cohorts of EPT children were based on extremely low birth weight (ELBW), <1000g, because GA measures were judged unreliable (Anderson, 2014).

Before the widespread use of assisted ventilation in the 1970s, there were few survivors of birth before 28 weeks' GA (Saigal and Doyle, 2008) and this is still the case in many low-income countries. In subsequent decades, significant advances in neonatal and obstetric care transformed the management of EPT birth, notably: regionalisation to optimise delivery in tertiary centres, antenatal corticosteroids, surfactant, continuous positive airway pressure (CPAP), magnesium sulphate and developmental care (American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine, 2017; Cheong et al., 2020; Saigal and Doyle, 2008; Stoll et al., 2015). Initial discoveries focused on treating pulmonary immaturity (Patel, 2016; Stoll et al., 2015), leading to strikingly improved survival after EPT birth by the mid-1990s (Saigal and Doyle, 2008). Survival rates have continued to increase in more recent decades in most high-income countries with improvements in neonatal intensive care and more active management of babies born EPT (Cheong et al., 2020; Morgan et al., 2022; Patel, 2016; Saigal and Doyle, 2008).

In the Victorian Infant Collaborative Study in Australia which constituted several population-based cohorts of babies with BW <1000g, survival rates to two-year corrected age for live births between 22 and 27 weeks' GA rose from 53% in the 1991-1992 cohort to 73% in the 2016-2017 cohort (Cheong et al., 2021). In France, survival to two-year corrected age for live births between 22 and 31 weeks' GA increased from 79.4% to 84.1% between the EPIPAGE (births in 1997) and the EPIPAGE-2 (births in 2011) studies (Pierrat et al., 2017). Steeper improvements were observed for infants born at 25-26 weeks' GA for whom survival

rates increased by more than 15% between 1997 and 2011. In the United States, the National Institute of Child Health and Human Development Neonatal Research Network compared survival at 18-22 months' corrected age in infants born periviable, i.e., 22-24 weeks' GA (Younge et al., 2017). Survival increased from 30% in epoch 1 (births in 2000-2003) to 36% in epoch 3 (births in 2008-2011). However, even with these improvements in survival, children born VPT, representing 1.5-2% of all births (Blencowe et al., 2012), still account for half of all infant deaths, i.e., more than 80 times the rate for full-term infants (Matthews et al., 2015).

The survival rate for EPT children is inversely associated with GA (Morgan et al., 2022; Patel, 2016), as illustrated by Patel (2016) in **Figure 1**, which compares several studies on EPT children. This figure also shows large variations in survival between countries, which – at least at the earliest gestational ages – have been related principally to differences in the active management of these babies and ethical decisions (Smith et al., 2017; Stoll et al., 2015).

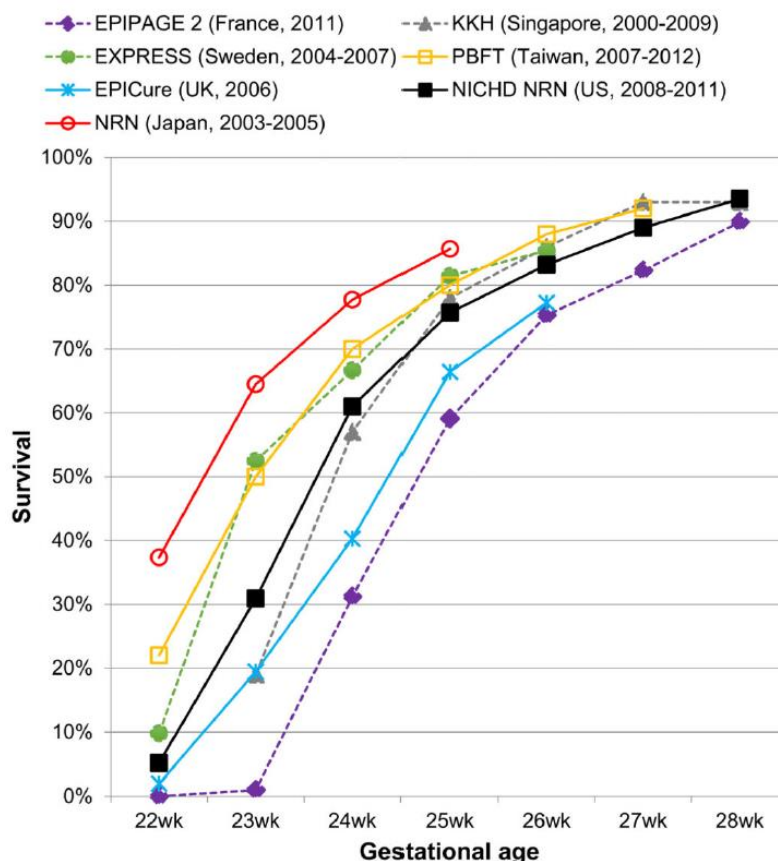


Figure 1. Gestational Age Specific Survival for Extremely Preterm Infants. Extracted from Patel (2016).

EPIPAGE-2, Etude Epidémiologique sur les Petits Ages Gestationnels 2. EXPRESS, Extremely Preterm Infants in Sweden Study. NRN, Neonatal Research Network. NICHD, National Institute of Child Health and Human Development. KKH, KK Women’s and Children’s Hospital. PBFT, Premature Baby Foundation of Taiwan. UK, the United Kingdom. US, the United States.

Complete reference: Patel RM. Short- and Long-Term Outcomes for Extremely Preterm Infants. *Am J Perinatol* 2016;33:318–28. <https://doi.org/10.1055/s-0035-1571202>.

2.1.2. Consequences of extremely preterm birth

Infants born EPT are biologically immature with all organs underdeveloped and particularly the brain and the lungs (Jobe and Bancalari, 2001; Rees and Inder, 2005), leading to high rates of short- and long-term neurological and medical problems (Patel, 2016; Saigal and Doyle, 2008). EPT infants have more hospital readmissions and other health problems in the weeks and years after discharge than infants born at term (Saigal and Doyle, 2008). Morbidities during the neonatal hospitalisation are strong predictors of death or disability after discharge (Patel, 2016; Schmidt et al., 2015).

Neonatal morbidities

Among survivors, rates of neonatal morbidities, many of which are unique to the preterm population, are high, in particular at lower GA (Patel, 2016; Saigal and Doyle, 2008; Stoll et al., 2015, 2010).

First, EPT birth results in the loss of months of growth in utero when most brain development occurs and consequently these infants are susceptible to medical complications and risks of disrupted brain maturation, leading to reduced brain volume and myelination (Ream and Lehwald, 2018; Rogers and Hintz, 2016). Other factors which commonly occur in preterm infants alter brain development, including prenatal hypoxic/ischaemic injury and inflammatory/infectious insults (Rees and Inder, 2005; Rogers and Hintz, 2016; Volpe, 2009a). These adverse consequences are more pronounced earlier in gestation and animal models suggest potential synergistic effects (Rees and Inder, 2005); i.e., the preterm birth affects the normal processes of brain maturation while the brain is also trying to repair hypoxic, ischaemic and inflammatory injuries (Rogers and Hintz, 2016). Thus, neurological consequences, in association with cerebral immaturity but also potentially synergistic hypoxic/ischaemic and inflammatory/infective insults (Rees and Inder, 2005; Rogers and Hintz, 2016; Volpe, 2009a) are commonly observed among infants born EPT (Patel, 2016; Saigal and Doyle, 2008).

Severe brain morbidities include intraventricular haemorrhage (IVH) and cystic periventricular leukomalacia (cPVL). The first is the most common type of intracranial haemorrhage with bleeding inside the lateral ventricles, and the second is defined by a necrosis of white matter in the brain (Volpe, 2009a, 2009b). Both have a strong impact on the prognosis of the infant during the neonatal hospitalisation as well as on neurodevelopmental impairments (NDI) including CP, cognitive and non-CP motor problems in childhood (Bolisetty et al., 2014; Gilard et al., 2020; Hintz et al., 2015; Linsell et al., 2016).

Secondly, pulmonary problems due to lung immaturity, namely newborn respiratory distress syndrome, are an important cause of death among infants born EPT (Patel, 2016; Stoll et al., 2015). The EPT infant's lungs are not fully developed and cannot provide enough oxygen due to lack of surfactant production which occurs between 24 and 28 weeks of gestation. To accelerate lung maturation, antenatal corticosteroids are administered when possible. Postnatally, infants are provided respiratory support and additional oxygen, however, this support may also injure the lungs and constitutes a risk factor for bronchopulmonary dysplasia (BPD) (Jobe and Bancalari, 2001), defined as the need for supplemental oxygen and/or ventilatory support at 36 weeks' postmenstrual age. BPD is the most common serious morbidity affecting infants born EPT (Jobe and Bancalari, 2001; Patel, 2016), and is strongly related to GA with a prevalence around 70% for infants born at 24 weeks' GA and 35% for infants born at 27 weeks' GA (Stoll et al., 2010). Adverse consequences associated with BPD persist throughout adolescence and adulthood, including airway hyperactivity, decreased lung function and airway obstruction (Jobe and Bancalari, 2001; Patel, 2016).

Several other common neonatal morbidities exist and have an impact on long-term prognosis. Infants born EPT are at risk of infection which may potentially cause death. These neonatal infections are divided into two categories: early onset sepsis with infection in the three first days of life related to maternal-fetal transmission and late onset sepsis with infection after three days of life coming from the hospital environment (Shane et al., 2017). For survivors, infections are associated with worse growth and long-term neurodevelopmental outcomes (Patel, 2016). Necrotising enterocolitis (NEC) is a necrosis of gastrointestinal tissues affecting one in 10 EPT infants (Edstedt Bonamy et al., 2019; Stoll et al., 2010). NEC has a high cause-specific mortality and survivors commonly have long-term consequences including poor growth and NDI (Patel, 2016). Retinopathy of prematurity (ROP) is one of the most common morbidities in infants born before 26 weeks' GA (Saigal and Doyle, 2008). The retina, developing late in pregnancy, is not fully vascularised in case of EPT birth. In addition, the infant is exposed to much higher oxygen concentration in the room air or incubator than in the womb, leading to the suppression of vascular endothelial growth factor and delaying retinal vascular growth (Chen and Smith, 2007; European Foundation for the Care of Newborn Infants, 2020). The excessive supplemental oxygen administration might also amplify this phenomenon. ROP has a direct impact on visual acuity and is the leading cause of blindness in infants born EPT (Patel, 2016).

Long-term health and developmental outcomes

Neonatal morbidities are major risk factors for long-term health and developmental impairments (Mangin et al., 2017; Patel, 2016; Rogers and Hintz, 2016; Saigal and Doyle, 2008; Tran et al., 2005), but even children without severe neonatal morbidity are vulnerable to the long-term sequelae of EPT birth. Health and developmental problems comprise cognitive impairment, CP and non-CP motor problems, behavioural problems, sensory impairments (visual and hearing deficits) and cerebro-visual impairments, and respiratory difficulties (Allotey et al., 2018; Doyle et al., 2021; Patel, 2016; Rogers and Hintz, 2016; Saigal and Doyle, 2008; Van Hus et al., 2014). Overall between 30% and 70% of children born EPT will develop a NDI (Pierrat et al., 2021, 2017; Younge et al., 2017). Similar to risks for neonatal morbidities, rates of long-term impairment and health difficulties are highest in the most immature survivors (Saigal and Doyle, 2008), as illustrated by Patel (2016) in **Figure 2**, presenting the spectrum of disability among infants surviving after birth before 27 weeks' GA for three studies.

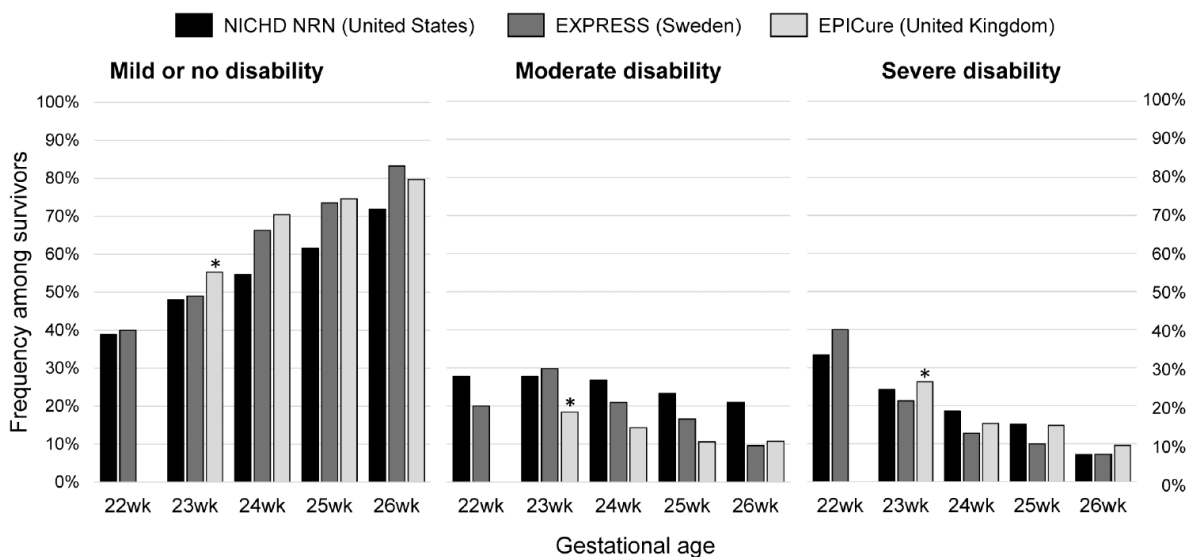


Figure 2. The Spectrum of Disability Among Surviving Extremely Preterm Infants. Extracted from Patel (2016).

NICHD, National Institute of Child Health and Human Development. NRN, Neonatal Research Network. EXPRESS, Extremely Preterm Infants in Sweden Study. wk, weeks.

*Estimates reported for infants ≤ 23 wk gestational age.

Complete reference: Patel RM. Short- and Long-Term Outcomes for Extremely Preterm Infants. *Am J Perinatol* 2016;33:318–28. <https://doi.org/10.1055/s-0035-1571202>.

This doctoral work focuses on the motor consequences of EPT birth, namely CP and non-CP MD, but these need to be investigated and understood in the broader context of the health and developmental risks facing these children who often have multiple problems. This is important because some impairments complicate screening and detection of motor problems, such as visual, hearing or severe cognitive deficits. Further, many perinatal and neonatal factors increase risks for a wide range of long-term outcomes and these comorbidities need to be considered when assessing overall impact of developmental motor problems on functional status and quality of life among preterm births.

Based on the EXPRESS population-based cohort study of EPT infants (<27 weeks) born in 2004-2007 (Sweden), mean intelligence quotient (IQ) score at 6.5 years of age was 14.2 points lower for children born EPT in comparison with a matched control group born at term (Serenius et al., 2016). Doing an umbrella review (i.e., a review of systematic review and meta-analysis) and a meta-regression analysis of which 25 studies were restricted to children born EPT/ELBW, Sentenac et al. (2022) found a pooled standardised mean difference and 95% confidence intervals (CI) of -0.94 (-1.07; -0.82) compared to term-born controls, which corresponds to an IQ deficit of approximately 14 IQ points.

These cognitive difficulties have direct consequences on academic performance and achievement (Hutchinson et al., 2013; Twilhaar et al., 2018). In a systematic review exploring the effect of preterm birth on school performance of school-age children with the majority of the articles included looking at VPT children, only one out of 16 studies did not find an association between prematurity and school performance (Moreira et al., 2014). Cognitive difficulties, shown to be common among EPT children at school age (Marlow et al., 2005; Serenius et al., 2016), continue into adulthood (Doyle and Anderson, 2010; O'Reilly et al., 2020), even if a partial catch-up may exist in adolescence (Luu et al., 2011).

Behavioural problems, usually detected or confirmed in preschool and elementary school, are mostly manifested by inattention, hyperactivity and anxiety, and likely interact with cognitive impairments to affect academic performance (Rogers and Hintz, 2016). Children born EPT are four-times more likely to be diagnosed with attention deficit hyperactivity disorder (ADHD) than full-term children (Johnson and Marlow, 2011; Scott et al., 2012). They are also more frequently diagnosed with autism spectrum disorder (ASD), depression or generalised anxiety, compared with children born at term (Johnson et al., 2010; Rogers and Hintz, 2016). These results were confirmed in the systematic review by Moreira et al. (2014) on the effect of preterm birth on behaviour among school-age children. Indeed,

most studies included in this review (18 out of 20) demonstrated an association between preterm birth and behavioural problems (Moreira et al., 2014).

Sensory impairments, mainly visual and hearing impairments, are much more common among children born EPT than their term-born peers (Jarjour, 2015; Molloy et al., 2013; Serenius et al., 2016). For instance, as mentioned previously, ROP can lead to blindness in infants born EPT (Patel, 2016). Hearing loss and deafness are less strongly associated than other morbidities with lower GA and BW, although this pattern is also seen (Hirvonen et al., 2018; Moore et al., 2012; Pierrat et al., 2021). Among children born EPT, severe sensory impairments (blindness, deafness which cannot be corrected with aides) have a low prevalence with a rate around 1-2% for each (Pierrat et al., 2021; Serenius et al., 2016). In addition, cerebro-visual impairments linking disturbances of both cerebral and visual development, have been less studied in the literature. These impairments are interconnected as visual function serves as the basis for the early development of several developmental milestones, including sensory-motor and cognitive skills (Atkinson and Braddick, 2007; van Veen et al., 2019).

Long-term respiratory health and pulmonary function is also affected by EPT birth, with a greater likelihood of upper and lower respiratory illnesses than term-born children over the first years of life (Gibson and Doyle, 2014). Hennessy et al. (2008) found that children born before 26 weeks' GA in the EPICure cohort (the United Kingdom) and with BPD had worse respiratory health over the first six years of life; with more respiratory symptoms and medication use at 30 months and six years compared to children without BPD. Peak expiratory flow at six years was lower for EPT children than classmates matched on age and sex, and with the lowest values for children discharge home with oxygen and those with BPD. In early adulthood, EPT survivors had worse pulmonary functions than term controls (Doyle and Anderson, 2010). Asthma has also been reported to be more frequent in children and young adults born EPT than term-born controls, but results have not been consistent in all studies (Doyle and Anderson, 2010; Gibson and Doyle, 2014; Hadchouel et al., 2018).

As shown in this overview children born EPT are a high-risk group with multiple health and developmental problems (Patel, 2016) which have continuing effects in childhood, adolescence and adulthood (Doyle and Anderson, 2010; de Kieviet et al., 2009; Patel, 2016). Contrary to observed declines in survival rates and short-term morbidities, related to progresses in neonatal and obstetric care, many of these long-term health and developmental outcomes for EPT children do not seem to have improved in high-income countries since the

mid-1990s (Cheong et al., 2020). In this context, understanding the long-term motor consequences of EPT birth, their risk factors, medical management and impact on the daily activities of children, is crucial to providing responses and support to families, health care professionals and individuals born EPT.

2.2. Developmental motor problems

Alongside the other long-term impairments described in the previous section, developmental motor problems, comprising CP, DCD and other MD are among the most common consequences of EPT birth (Adams-Chapman et al., 2018; Baron and Rey-Casserly, 2010; Bolk et al., 2018; Hafström et al., 2018; de Kieviet et al., 2009; Linsell et al., 2016; Spittle et al., 2018; Williams et al., 2010). As described in the introduction, CP is defined as “a group of permanent disorders of the development of movement and posture, causing activity limitation, which are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain” (Rosenbaum et al., 2007, p5). On the other hand, non-CP developmental motor problems are manifested by “motor deficits in coordination, balance, gross and fine motor control, and visual motor integration” (Spittle and Orton, 2014).

2.2.1. General pathogenesis of developmental motor problems

Aetiological and neurobiological mechanisms

The disturbance of brain function caused by the interruption of normal brain genesis and potential focal brain injuries following EPT birth affect motor function (Bracewell and Marlow, 2002; Ream and Lehwald, 2018; Volpe, 2009a). Preterm birth interrupts normal brain maturation processes, including neuronal migration, synaptogenesis, myelination and cytological maturation (Rogers and Hintz, 2016; Volpe, 2009a). In addition, altered early extra-uterine sensory and movement experiences (e.g., light and sounds, gravity) may interfere with normal musculoskeletal and brain development (Ream and Lehwald, 2018; Spittle and Orton, 2014). Lastly, some postnatal biological factors may directly impact motor development (insufficient growth or small muscle size, for instance), and may also affect brain maturation (Spittle and Orton, 2014). This abnormal development over the first year may resolve or evolve into clear neuromotor problems (Bracewell and Marlow, 2002).

Infants born VPT have impaired brain growth and delayed maturation compared with term-born peers (Keunen et al., 2016), with reduced brain volume persisting into adolescence

and adulthood (Ream and Lehwald, 2018). In addition, as reported by Spittle et al. (2011) in several articles using magnetic resonance imaging (MRI) in the neonatal period, most children born VPT display diffuse white matter abnormalities (WMA), including white matter signal abnormality, loss of white matter, ventricular dilatation, and thinning of the corpus callosum (Boardman et al., 2010; Dyet et al., 2006; Inder et al., 2003; Woodward et al., 2006). WMA are predictive of early motor delay and CP (Miller et al., 2005; Woodward et al., 2006). Research on EPT/ELBW adolescents also found that they had higher corticospinal tract and lower primary motor cortex thickness than the comparison group (Kelly et al., 2015). Children with CP had higher corticospinal tract diffusivities (correlated with primary motor cortex volume and area) than EPT/ELBW adolescents without motor impairment. By connecting cerebral cortical regions, including the motor cortex, and spinal cord motor neurons, the corticospinal tract is critical for motor function (Kelly et al., 2015).

Whereas, the neural mechanisms involved in CP are varied, they always involve an early alteration to the developing brain (Ream and Lehwald, 2018; Rosenbaum et al., 2007; Volpe, 2009a). In addition, there is evidence that the location of the brain lesion may be important (Tran et al., 2005). Thus, the incidence of cPVL is highly predictive of CP (Spittle and Orton, 2014). In addition, children who experience severe respiratory distress are also susceptible to white matter damage and subsequently CP (Tran et al., 2005).

On the other hand, the mechanisms for other non-CP motor problems in preterm children are less clear (Spittle and Orton, 2014; Zwicker et al., 2012). This was reported by Zwicker et al. (2012) in a review on DCD, but it is true for other non-CP motor problems related to preterm birth (Spittle and Orton, 2014). The aetiology is largely unknown, but may be related to central nervous system pathology (Ferrari et al., 2012). “Minimal neurological dysfunction,” which reflects “a distinct form of perinatally acquired brain dysfunction, which is likely associated with a structural deficit of the brain” has been proposed to result from the stress associated with preterm birth (Holsti et al., 2002; Zwicker et al., 2012). Using MRI at term-equivalent age to estimate WMA and assessing motor functions at five years among 193 VPT children, Spittle et al. (2011) found WMA predictive of motor impairment in VPT children. Compared with no WMA, mild WMA increased the odds for moderate to severe motor impairment five-fold and for mild to severe motor impairment two-fold, and moderate to severe WMA increased the odds for moderate to severe motor impairment 19-fold and for mild to severe motor impairment nine-fold. Their results remained similar after controlling for potential confounders and excluding children with CP (n=14). Keunen et al. (2016) also found

unmyelinated white matter volume to be associated with worse motor outcomes at 24 months using >100 children born VPT. In another study, children without CP and at risk of DCD displayed smaller brain volumes at term equivalent age and seven years, and altered white matter microstructure at seven years (Dewey et al., 2019). These results suggest that alterations in brain volume were present as early as term equivalent age and persisted throughout early childhood (Dewey et al., 2019).

2.2.2. Clinical manifestations

Clinically, three major classifications are applied to CP: motor-type (spasticity, dyskinesia, ataxia, hypotonia), topography (hemiplegia, diplegia, quadriplegia/tetraplegia) and function (McIntyre et al., 2011). The last classification, the gross motor function classification system (GMFCS) (Palisano et al., 1997), is the gold standard for describing motor function in CP children (McIntyre et al., 2011). GMFCS is a five-level classification system based on the person's ability to self-initiate movement with a focus on sitting, transferring, and mobilising (Palisano et al., 1997). It provides a common language that produces a "picture" of a child with CP (McIntyre et al., 2011). Different classification descriptions exist for different age groups and for children included in this doctoral work, aged five to six years, the levels are as follows: i) walks without restrictions, limitations in more advanced gross motor skills; ii) walks without restrictions, limitations walking outdoors and in the community; iii) walks with assistive mobility devices, limitations walking outdoors and in the community; iv) self-mobility with limitations, children are transported or use power mobility outdoors and in the community; and v) self-mobility is severely limited, even with the use of assistive technology.

For non-CP MD, there are multiple deficits across several aspects of motor control (including planning and anticipatory control of movement), basic processes of motor learning (including procedural learning), and cognitive control (or executive function) (Blank et al., 2019; Wilson et al., 2017). In a recent systematic review including behavioural data from 91 studies, Wilson et al. (2017) showed that task type and difficulty moderate these motor difficulties. Furthermore, they reported that children can adopt motor compensatory strategies/actions to overcome constraints and carry out tasks, even if this is not done in the most efficient way (Blank et al., 2019; Wilson et al., 2017).

In the early months of life, global developmental delay and CP present similar delayed acquisition of developmental milestones, both with functional impairments (McIntyre et al., 2011). However, CP cannot be considered as a "delay" as children will not "grow out of it"

(McIntyre et al., 2011). The GMFCS classification system is unstable in the two first years of life, especially for ambulant CP, and reassessment is recommended after two years of age to have a more accurate description of function and severity (Gorter et al., 2009; McIntyre et al., 2011; Surveillance of Cerebral Palsy in Europe, 2000). For non-CP MD, even if it is important to have the earliest possible detection to take advantage of the developmental window of maximum brain plasticity in the first years of life, four to five years of age appears to be the minimum for accurately distinguishing between normal trajectories, slow motor development and abnormal motor development (especially when disturbances are small) (Ferrari et al., 2012; McIntyre et al., 2011), taking into consideration the “catch-up” of some children in their early years and the reliability of tools assessing motor skills (Blank et al., 2019; Spittle and Orton, 2014). Ultimately, the physical disability of CP is life-long, while non-CP motor problems appear to manifest more strongly in the developmental window during which children are learning key motor skills such as dressing independently, ball catching, and handwriting (McIntyre et al., 2011).

2.2.3. Prevalence of cerebral palsy and non-cerebral palsy movement difficulties

Prevalence of non-cerebral palsy movement difficulties

While it is now well-known that children born VPT, including children born EPT, are more likely to have non-CP MD compared to their term-born peers (Edwards et al., 2011; de Kieviet et al., 2009; Williams et al., 2010), there are important discrepancies in the estimation of rates of these difficulties between studies with variations from around 10% to more than 40% (Bolk et al., 2018; Bos et al., 2013; Setänen et al., 2016; Spittle et al., 2021). These differences are at least partially explained by large methodological variability in the literature. Most studies include children born VPT and not specifically EPT and population inclusion criteria with GA and/or BW thresholds vary widely. For instance, in the review by Evensen et al. (2020), only 14 out of 38 studies specifically report outcomes for children born EPT/ELBW. In addition, data span a long time period with the birth years of participants ranging from 1976 to 2007 and only 13 out of the 38 studies with a birth year ≥ 2000 (Evensen et al., 2020). Furthermore, studies use multiple tools to estimate non-CP MD which could affect prevalence estimates. While, the Movement Assessment Battery for Children, 1st or 2nd Edition (MABC, MABC-2) is the most common tool, e.g., 25 out of the 38 studies in the review by Evensen et al. (2020), or nine out of 15 studies in the review by Williams et al. (2010), many other tools are used: Bruininks-Oseretsky Test of Motor Proficiency, Peabody Developmental Motor Scales,

Rivermead Motor Assessment, Test of Motor Impairment, Zurich Neuromotor Assessment, Developmental Coordination Disorder Questionnaire, etc. (Blank et al., 2019; Evensen et al., 2020; Williams et al., 2010) In addition, different cut-off points are used to define the (category of) motor impairment: $<5^{\text{th}}$ or $\leq 5^{\text{th}}$ percentile, $<10^{\text{th}}$ percentile, $<15^{\text{th}}$ or $\leq 15^{\text{th}}$ percentile, <-2 standard deviation (SD), <-1.5 SD, <-2 SD (Evensen et al., 2020; Williams et al., 2010). A final point is study sample sizes which vary and can be small. For example, looking at the two previous reviews trying to estimate a prevalence, the sample size of the included studies varied between 36 and 396 participants, with five being over 150 out of the nine studies in Williams et al. (2010); and between 10 and 371 participants, with 14 being over 150 out of the 38 studies in Evensen et al. (2020).

These variations in rates, tools and in cut-offs are illustrated in [Figure 3](#), taken from Evensen et al. (2020). They show that the prevalence of non-CP motor problems among VPT/very low birth weight (VLBW, i.e., $<1500\text{g}$) individuals assessed by the MABC/MABC-2 varied from 7.9% to 37.1% in studies using a cut-off at the 5th percentile, and from 12.2% to 70.6% in studies using a cut-off at the 15th percentile (Evensen et al., 2020). Similar variations in prevalence were observed in a systematic review specifically on the prevalence of motor impairment in preterm children without CP (Williams et al., 2010). Using the terms of mild-moderate and moderate motor impairment to define children at risk for MD and with significant MD, respectively; Williams et al. (2010) found a pooled estimate of 19.0% for children with moderate impairment and 40.5% for mild-moderate impairment. However, the authors were again interested in VPT children (and preterm children up to 34 weeks' GA in one study) and not only on children born EPT who have higher risk of MD.

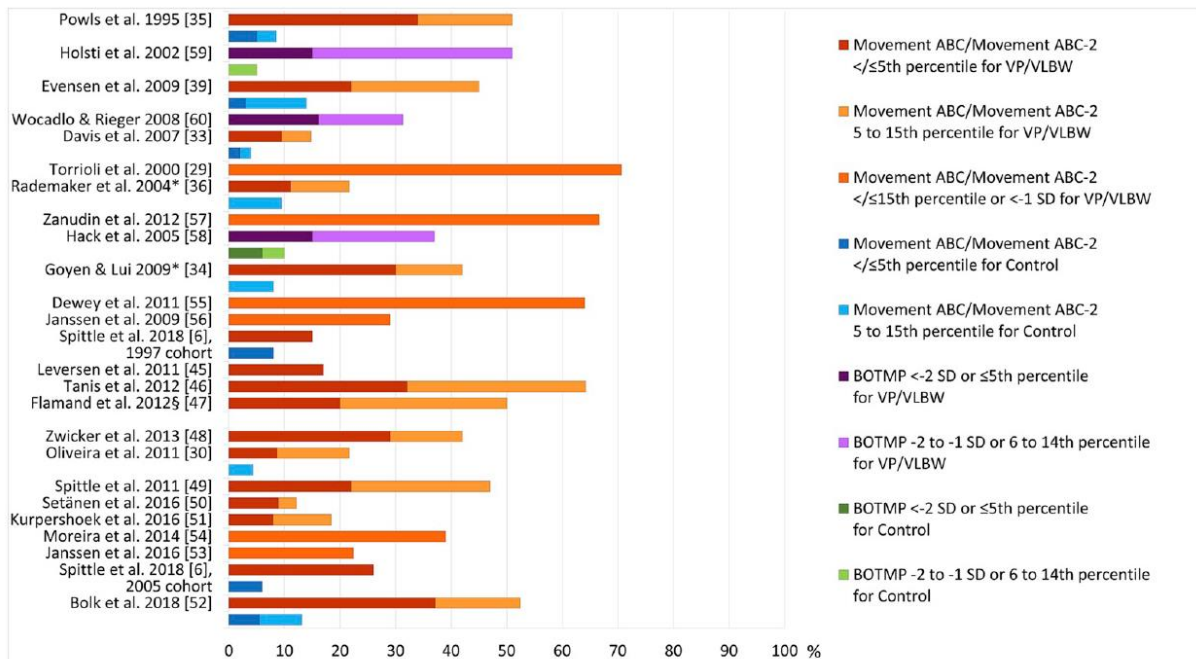


Figure 3. Prevalence of motor problems in VPT/VLBW individuals assessed by using various motor tests and cut-offs in the order of years of birth of the study participants. Extracted from Evensen et al. (2020).

BOTMP, Bruininks-Oseretsky Test of Motor Proficiency. Movement ABC/ABC-2, Movement Assessment Battery for Children/Second Edition. SD, standard deviation. VLBW, very low birth weight. VP, very preterm.

*No controls <5th percentile. §No controls ≤5th or 15th percentile.

Complete reference: Evensen KAI, Ustad T, Tikanmäki M, Haaramo P, Kajantie E. Long-term motor outcomes of very preterm and/or very low birth weight individuals without cerebral palsy: A review of the current evidence. *Semin Fetal Neonatal Med* 2020;25:101116. <https://doi.org/10.1016/j.siny.2020.101116>.

Prevalence of cerebral palsy

CP is a well-documented consequence of EPT birth with around half of children with CP being born preterm (Demeši Drljan et al., 2016; Kirby et al., 2011). Less frequent than non-CP MD, CP is more severe, demonstrated by the fact that 40% of children with a CP diagnosis cannot walk independently (Korzeniewski et al., 2018). As illustrated by a meta-analysis of 25 studies conducted by Himpens et al. (2008), CP prevalence is directly related to the degree of prematurity. They found a prevalence of 14.6% for children born at 22-27 weeks' GA (based on seven studies), 6.2% for those born at 28-31 weeks' GA, 0.7% for those born at 32-36 weeks' GA, and 0.1% for children born at term. Thus, CP occurs more than 100-times more often among EPT than term-born children, with a prevalence between 7% and 20% (Hafström et al., 2018; O'Shea, 2008), and with estimates around 9 to 12% in main population-based cohort studies, e.g., EPICure (Marlow et al., 2005), EPIPAGE 1 (Beaino et al., 2010), EPIPAGE 2 (Pierrat et al., 2021), EXPRESS (Hafström et al., 2018). Using a network with >2,000 EPT children, Adams-Chapman et al. (2018) reported 12% of children diagnosed with CP. In two

meta-analyses that aimed to update knowledge on the prevalence of CP, Oskoui et al. (2013) and Pascal et al. (2018) found a rate of 8.2% and 10.0% for children born before 28 weeks' GA, respectively.

Trends in prevalence over the last decades

Evidence from population-based samples and CP registers in Australia, Europe and the United States describing trends in prevalence, subtypes, and severity, suggest that the frequency of CP in EPT infants has been decreasing for several decades (Galea et al., 2019; Li et al., 2019; Platt et al., 2007; Reid et al., 2016; Surveillance of Cerebral Palsy in Europe, 2000), with a more significant decrease in moderate to severe CP (Platt et al., 2007; Reid et al., 2016). For instance, in the Australian CP register, severity of CP decreased for infants born ELBW; percentages of children with bilateral CP compared with unilateral CP decreased incrementally from 72.2% (births in 1995-1997) to 55.8% (births in 2007-2009) (Cheong et al., 2020; Galea et al., 2019). Similar overall trends have been reported from 1996 to 2009 in South Carolina in the United States, but with fluctuations between years (Li et al., 2019). The two meta-analyses by Oskoui et al. (2013) and Pascal et al. (2018), found rates of 8.2% and 10.0%, respectively, lower than the previous meta-analysis by Himpens et al. (2008), where the prevalence was 14.6%.

In parallel, however, non-CP MD rates among children born EPT seem to have increased (Cheong et al., 2020; Spittle et al., 2018). For instance, Spittle et al. (2018) found that rates of children with non-CP MD (named non-CP motor impairment) at eight years' corrected age increased over time from 13% in 1991-1992, to 15% in 1997 and to 26% in 2005, while rates of CP remained relatively constant in three different cohorts that were part of the Victorian Infant Collaborative Study, a series of longitudinal, population-based studies of children born EPT/ELBW in Victoria, Australia.

The estimation of the prevalence of developmental difficulties could also depend on the timing of the measure. Development is a continuous and dynamic process of changes with improvements in the acquisition and development of abilities in different developmental areas including cognition, language, motor function, behaviour and others (Vieira and Linhares, 2011). However, these dynamics may change over time (Patel, 2016). For instance, when comparing the severity of disability at 30 months and six years of age in the EPICure study (i.e., children born <26 weeks' GA), Marlow et al. (2005) found that approximatively two

in five infants who were diagnosed with severe disability at 30 months no longer had severe disability at six years of age. In contrast, they found that one in four infants without any disability at 30 months were found to have a moderate or severe disability at six years (Patel, 2016). In addition, O'Shea (2008) emphasises the fact that the diagnosis of CP is based on a clinical assessment (and not on laboratory testing or neuroimaging); and while the underlying abnormality of the brain is presumed to be permanent and non-progressive (Rosenbaum et al., 2007), evidence that clinical manifestations and severity of functional impairment may change over time exist.

2.2.4. Risk factors for cerebral palsy and non-cerebral palsy movement difficulties

Risk factors for non-cerebral palsy movement difficulties

The risks of developing non-CP MD are strongly associated with decreasing GA at birth (Evensen et al., 2020; Ferrari et al., 2012; de Kieviet et al., 2009). Several other perinatal and neonatal factors have been reported in the literature, but results are sparse and inconsistent. For instance, premature rupture of membranes (PROM) (Goyen and Lui, 2009), brain lesions (including severity grade) (Hollebrandse et al., 2021; Jansen et al., 2021; Lean et al., 2018), confirmed sepsis (Lean et al., 2018), BPD (Dewey et al., 2011), postnatal corticosteroids (Dewey et al., 2011), NEC (Taylor et al., 2006), ROP (Goyen and Lui, 2009), have been identified as risk factors in some studies only. Results on sociodemographic risk factors for non-CP have also been inconclusive (Evensen et al., 2020; van Hoorn et al., 2021; Linsell et al., 2016). High level of social risk was associated with poorer cognitive outcomes at two and five years, this was not the case for motor outcomes in a study by Lean et al. (2018). Van Hoorn et al. (2021) found an inconsistent association between sociodemographic factors and non-CP MD, mostly described in terms of parental education and profession, with worse socioeconomic status associated with increased risk in only one of five studies.

Recent reviews concluded that “relatively few early life factors were consistently associated with motor impairment in childhood” (van Hoorn et al., 2021, p515), and “male sex (as well as preterm birth) emerged as the only risk factor for which there was evidence of an association with motor impairment in children free of major disability” (Linsell et al., 2016, p565). Some of this inconsistency likely results from differences between the studies included in these reviews, i.e. GA inclusion criteria, inclusions or exclusion of other severe disabilities or CP, etc. For instance, only two of 28 studies in a recent systematic review on prognostic factors for CP and motor impairment in children born VPT/VLBW from Linsell et al. (2016)

were restricted to EPT children. This systematic review included seven studies with a mean sample size of 169 (range 48-371) reporting risk factor analyses of motor impairment for VPT (or VLBW) children free of major disability (CP or severe neurosensory impairment excluded) and assessed at five years of age or older.

Risk factors for cerebral palsy

The degree of prematurity and several other perinatal and neonatal risk factors for CP in preterm infants are documented in the literature (van Lieshout et al., 2017; Linsell et al., 2016; McIntyre et al., 2011; Rogers and Hintz, 2016). Perinatal and neonatal risk factors include severe brain lesions, male sex, sepsis, multiple gestation, surgery, postnatal corticosteroids and high-frequency ventilation. Cerebral lesions and in particular cPVL and grade IVH III and IV are the most important predictors of CP in VPT infants (Beaino et al., 2010; Himpens et al., 2010; Spittle and Orton, 2014; Tran et al., 2005). In the systematic review by Linsell et al. (2016), nine out of the 12 studies that included brain injury in their final models found it to be predictive of CP. However, the evidence for the influence of lower grade 1 to 2 IVH remains limited. This review concluded that there was strong evidence that IVH and cPVL are prognostic factors for CP, with some evidence that postnatal corticosteroids increase CP risk, while antenatal corticosteroids reduce it. However, after adjustment on these factors, they found that the prognostic value of GA was limited. Reasons mentioned for reduced discriminatory power were that in cohorts restricted to earlier GA there is not a wide range of GA values and the existence of residual confounding by other clinical events. An outstanding question remains whether lower GA is a risk factor among the highest risk group of children born EPT after consideration of severe neonatal morbidities (Himpens et al., 2008; Linsell et al., 2016)

Results on sociodemographic risk factors vary. Eight out of the 12 studies included by Solaski et al. (2014) in their systematic review on the relationship between sociodemographic factors and the risk of CP, found low socioeconomic status to be a risk factor for CP, but only three detected statistically significant associations after controlling for BW and GA. In a systematic review of prognostic factors for both CP and (non-CP) motor impairment in children born VPT (and so EPT) (Linsell et al., 2016), only two out of 12 studies reported an association between sociodemographic factors and a higher risk of CP, namely lower maternal education and African-American origin (study in the United States).

2.2.5. Links with other developmental problems

Multiple developmental problems

Comorbidity of motor problems with other developmental problems is common (Pieters et al., 2012). For instance, Li et al. (Li et al., 2018) highlighted the link between physical and emotional/social development by showing that children with DCD experienced more internalizing problems compared to typically developing children. Similar results were reported on the co-occurrence of ADHD for up to 50% of children with DCD (Blank et al., 2012; Karras et al., 2019). Van Hus et al. (2014) found that among five-year-old children born <30 weeks' GA and/or ELBW with motor impairments (32% of the children), 58% had complex minor neurological dysfunctions, 54% had a low IQ, 69% had a slow processing speed, 58% had visuomotor coordination problems, and 27%, 50%, and 46% had conduct, emotional, and hyperactivity problems, respectively. Potharst et al. (2011) investigated 104 children born before 30 weeks' GA or ELBW and 95 term-born children on multiple tests (including the MABC-2) at five years corrected age and found that 75% of the preterm children had at least one disability with co-occurring disabilities in half of the children born preterm. This compared to 27% of term-born children with a disability and 8% with co-occurring disabilities. Research has also shown that hearing impairments, a common consequence of VPT birth, have a cumulative detrimental effect on the acquisition of language skills and learning at school (Saigal and Doyle, 2008; Taylor et al., 2004).

For CP, its definition as a pure motor impairment only is under debate because the various brain lesions causing the motor dysfunction are also often related directly or indirectly with several co-occurring impairments affecting vision and cognition, for example. (Himmelmann et al., 2006; Shapiro, 2004). Thus, in a systematic review and meta-analysis to summarise evidence on the rates of co-occurring difficulties with CP, Novak et al. (2012) found that among children with CP, "3 in 4 were in pain, 1 in 2 had intellectual disability, 1 in 3 could not walk, 1 in 3 had a hip displacement, 1 in 4 could not talk, 1 in 4 had epilepsy, 1 in 4 had a behaviour disorder, 1 in 4 had bladder control problems, 1 in 5 had a sleep disorder, 1 in 5 dribbled, 1 in 10 were blind, 1 in 15 were tube-fed, and 1 in 25 were deaf."

These co-occurring impairments in a significant proportion of children born EPT could result from and be influenced by multiple antenatal, perinatal and postnatal causes (Rogers and Hintz, 2016).

Causality or co-occurrence of motor problems with the other developmental problems?

An unresolved question is whether motor and other associated impairments have a common origin, thereby co-existing or whether motor impairments are a cause of later cognitive or other impairments because children with motor problems are limited in their interactions with their environment and have reduced opportunities to develop in other areas. This is the concept of affordance or possibilities for action (Gibson, 2014). Among ELBW children, the group classification of motor development at one year was predictive of cognitive performance at four years, independently of biological and social factors, or the presence of CP (Burns et al., 2004). At school age, difficulties with activities such as running or drawing have been shown to affect physical, social and academic performance (Spittle and Orton, 2014; Zwicker et al., 2013). For instance, ability to use one's hands appears to play a major role in early cognitive development (Dellatolas et al., 2003).

However, the mechanisms for these associations are uncertain and some authors argue that motor and cognitive development are fundamentally related processes involving similar parts of the brain (Burns et al., 2004), e.g., cerebellum and the prefrontal cortex (Diamond, 2000). The review of current evidence on the link between motor and cognitive development in children born preterm and/or with low BW (i.e., <2500g) by Oudgenoeg-Paz et al. (2017) concluded that, even if the studies included usually show a link between level and/or quality of motor development during the first year of life and later cognitive skills, the small number of studies (n=17) and the possible effect of early interaction between motor and cognition on this relation, more research is needed to understand the underlying causal pathways. Blank et al. (2019, p256) describes the underlying question in the context of DCD as follows: "a child from a culture, which limits physical activity or which provides little opportunity for motor learning may present like a child with DCD (at least initially). A child with ADHD might appear to have movement problems, which are in fact caused by impulsivity and/or inattention." They opt for the term "co-occurring" (consistent with the terms concurrent, overlapping) instead of "comorbid" to reflect the presence of two or more conditions without a known common aetiology. Indeed, whether the motor and cognitive difficulties are independent factors associated with preterm birth or one is a causative factor for the other is still not clear (Ferrari et al., 2012).

2.3. Impact of motor problems on children's day-to-day life

As described in the previous sections, CP and non-CP MD, even when MD are minor, have implications for many other areas of functioning, including cognitive development, school performance, social integration, and functioning in adulthood (Allotey et al., 2018; Davis et al., 2007; Moreira et al., 2014; O'Reilly et al., 2020; Oudgenoeg-Paz et al., 2017; Van Hus et al., 2014; Zwicker et al., 2013) with persistence into adolescence and into adulthood (Doyle and Anderson, 2010; Husby et al., 2016; Stahlmann et al., 2016). Given the potential for limitation in daily activities, schooling and social relationships, it is important to assess the consequences of these motor problems on children's well-being, yet this is not well described among children born EPT (Vederhus et al., 2010; Zwicker et al., 2013).

2.3.1. The definition of health-related quality of life

To understand the full health burden associated with motor difficulties among EPT, it is important to go beyond somatic indicators of health to assess how children feel, psychologically and physically, their relationships with other people and their abilities to cope with everyday life (Ravens-Sieberer et al., 2006). As defined by WHO, good health should be perceived as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" (World Health Organization, 1948).

Measures of quality of life (QoL), defined broadly as the "individual's perceptions of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, and concerns" (Vieira and Linhares, 2016; World Health Organization, 1995), have been developed to measure this broader definition of health. QoL has become an important outcome used with information on mortality and morbidity in epidemiology (Saigal and Tyson, 2008; Vieira and Linhares, 2016). Despite the slight variations in the definitions used in this literature, Eiser and Morse (2001a) identify three key elements that define the concept of QoL, namely, they i) are subjective and based on the perception of the individual; ii) reflect a multidimensional construct; and iii) can include both objective (i.e., what an individual can do) and subjective evaluations (Zwicker and Harris, 2008).

Within the more global construct of QoL, HRQoL focuses specifically on the impact of health (including disease, treatment, impairment) on an individual's well-being (Upton et al., 2008; Waters et al., 2009). In other words, HRQoL measures the level of interference of health limitations in day-to-day functioning (Eiser, 2004; Flapper and Schoemaker, 2008), by

simultaneously considering the physical, emotional and social dimensions of health and well-being (Eiser, 2004; Eiser and Morse, 2001a; Mottram and Holt, 2010; Zwicker and Harris, 2008).

2.3.2. Results reported in the literature

Health-related quality of life among children born preterm

Two systematic reviews have synthesised the literature on HRQoL among preterm children compared to term children. Zwicker and Harris (2008) conducted a systematic review on HRQoL in childhood and adulthood after preterm birth, with articles published up to September 2006. The six studies on preschool-aged children found lower HRQoL compared to the control group. The only study on school-aged children considered the health utility scores of children born ELBW and also found lower scores compared with their term-born peers. Similar results were found for adolescents but in young adulthood, differences remained in physical functioning only. Vieira and Linhares (2016) followed up on this review, including studies from 2007 and 2015, with 10 out the 22 articles included investigating the QoL in childhood. Parents of children who were born preterm reported worse well-being for their children compared with parents of children born at term. Only one study did not find statistically significant difference, but the children in this sample had higher GA (32-35 weeks' GA), had not required admission to the neonatal intensive care unit, and did not show any major behavioural problems (Ketharanathan et al., 2011).

Both of these reviews concluded that the effects of preterm/VLBW birth on HRQoL seem to diminish over time (Vieira and Linhares, 2016; Zwicker and Harris, 2008). The variation across age groups possibly reflects developmental changes, differences in the source of information (parental-report vs self-report), differing definitions of HRQoL, or true changes in HRQoL (Vieira and Linhares, 2016; Zwicker and Harris, 2008). Although parental-report is necessary for young children, it might be influenced by parents' feelings toward and expectations for their children. The review by Vieira and Linhares (2016) investigated assessment approaches and found that agreement between parents and their children was lower in younger age groups compared with older age groups. Agreement was relatively good on subjects related to physical health, involving the more observable aspects of the child's life such as illness or limitation of daily activities, while greater disagreement was observed for more subjective domains such as personal feelings or perceptions (Vieira and Linhares, 2016).

Since this last systematic review, additional studies have been published with some of them specifically on children born EPT. Peart et al. (2021) found that children in the post-surfactant era had clinically important reductions in HRQoL compared with full-term controls. They used data from the Victorian Infant Collaborative Study in Australia and analysed parent-completed health utilities index at eight years of age for 475 EPT and 570 term-born controls in three different cohorts: birth in 1991-1992, 1997 and 2005. A study in France by Gire et al. (2019) observed that the QoL of school-aged EPT children without severe impairment was lower compared to a reference population from both the parent's and child's point of view. Using 155 VLBW infants and 129 full-term controls and with the 17-Dimensional questionnaire to assess HRQoL at eight years, the HRQoL of healthy VLBW children did not differ from the controls (Huhtala et al., 2016). However, VLBW children with one or more morbidities had lower scores in several HRQoL dimensions.

This latter result reminds us that it is likely that the HRQoL could be also associated with health or developmental status and not only the degree of prematurity. With this idea in mind, Saigal et al. (2016) looked at the HRQoL trajectories of ELBW survivors and a group of normal BW controls at three ages, i.e., 12-16 years, 22-26 years, and 29-36 years. ELBW survivors were classified as to whether or not they had a neurosensory impairment, defined as a CP diagnosis, blindness, deafness and microcephaly, diagnosed at three years of age by a developmental pediatrician. ELBW survivors with a neurosensory impairment had consistently lower HRQoL compared with both ELBW survivors without neurosensory impairment and normal BW controls, from adolescence and into adulthood, while ELBW survivors without neurosensory impairment also had significantly lower HRQoL compared with normal BW controls. These last points are more in favour of a link between developmental problems and HRQoL, instead of a link between prematurity and developmental problems directly.

Health-related quality of life among children with developmental motor problems

Studies not specifically restricted to children born preterm, but focusing on children with motor problems also have relevance for our research questions. There are several systematic reviews summarising this research. Makris et al. (2021) and Zwicker et al. (2013) looked at the QoL in children and adolescents with CP and non-CP MD (termed DCD), respectively. For children with CP, physical QoL was affected compared to control children without CP, but inconsistent findings were reported between CP and psychological and social QoL depending on the measurement tool used (Makris et al., 2021). For children with DCD, most studies

reported significantly poorer results in physical, psychological and social functioning compared with their typically developing peers (Zwicker et al., 2013), including for children in the border-line range for MD (Zwicker et al., 2013). Recently, Karras et al. (2019) compared self- and parental-reported KidScreen-52 and Strength and Difficulties Questionnaire (SDQ) of 50 children with DCD aged around 10 years with normative data. Caregivers had a significantly lower perception of their child's HRQoL than children themselves. But both children with DCD and their parents reported significantly lower HRQoL compared to published norms in many domains. In line with these results, 11-year-old preterm children born $\leq 1500\text{g}$ with DCD reported lower self-experienced HRQoL (Uusitalo et al., 2020). Given the nature of DCD, it is not surprising that children with this disorder experience difficulties in the physical domain (Zwicker et al., 2013). However, as previously shown in the *section 2.2.5*, several other developmental problems can co-occur and have also been associated with poorer HRQoL (Huhtala et al., 2016; Natalucci et al., 2017). Thus, whereas children with DCD report lower HRQoL in several domains compared with typically developing children, discrepancies in results for psychological and social domains may be related to the presence or absence of comorbidities (Zwicker et al., 2013). Indeed, in their systematic review, Zwicker et al. (2013), they reported that over half of the studies (22 out of 41) did not report the presence or exclusion of comorbidities in their sample, making difficult to ascertain how co-occurring comorbidities influence the different HRQoL domains.

Most studies have focused on HRQoL in preterm populations (Vieira and Linhares, 2016; Zwicker and Harris, 2008), or among children with CP or DCD (Makris et al., 2021; Zwicker et al., 2013), and not specifically on how developmental motor problems among the EPT population could affect the child's everyday life. In the systematic review by Zwicker et al. (2013), despite the impact of DCD on multiple domains, only one study used a QoL measure as an outcome. Furthermore, in the systematic review on developmental outcomes and QoL in children born preterm from Vieira and Linhares (2011), QoL was an outcome in only two studies of preschool children and one study of school-aged children. As reported by Gire et al. (2019), when looking at the 37 studies on the HRQoL of preterm individuals included in the reviews from Saigal and Tyson (2008) or Vieira and Linhares (2016), five studies were on school-aged children born VPT and only three studies were on EPT children (for a total of 395 children). In addition, samples sizes are relatively small and varied widely between studies. In the systematic review from Zwicker et al. (2013) for instance, sample sizes ranged from six to

346 individuals, with most studies having a sample size between 20 and 50. By investigating 15 studies on the HRQoL of preterm populations, Zwicker and Harris (2008) reported a lack of methodological consistency, including the concept of QoL being measured, which reduces the possibility of comparing between studies. Therefore, while existing research provides some indication that HRQoL would be affected for children born EPT with motor problems, there is a need for further research targeting this population specifically.

2.4. Health care services for developmental motor problems

2.4.1. Interventions to improve motor performance

The first six years of life constitute a critical period of motor development with the reorganisation of the neural connections required for the acquisition of most motor skills in the postnatal period (Chakrabarty and Martin, 2010; Ferrari et al., 2012). Intervention in children detected with motor difficulties can take advantage of the neuroplasticity and ability to more efficiently reorganise neural connectivity in response to new experiences or training during this period (Chorna et al., 2020; Ferrari et al., 2012).

Early intervention to prevent CP and non-CP motor problems

As defined by Spittle et al. (2015), an early developmental intervention is a programme beginning within the first year of life, with or without an inpatient component, and with the aim of enhancing the child's development. These programmes may have different goals depending on the target public and the period, including prevention, remediation or treatment of a specific delay or disability. Thus, an intervention starting at an early age for infants at high risk of developmental problems may reduce the prevalence and severity of certain outcomes (Doyle et al., 2014; Spittle et al., 2015).

In a Cochrane review to estimate the effectiveness of early developmental intervention programmes in the high-risk preterm population, Spittle et al. (2015) found inconclusive results. With regards to motor outcomes, the meta-analysis of 12 studies showed a significant but small effect in favour of early intervention in infancy only. They found little evidence of a positive effect on long-term motor outcomes, but only five studies reported outcomes after infancy: three at preschool age and two at school age. No effect was found on the rate of CP among survivors and no studies reported on rates of DCD. However, only four out of 25 included (quasi) randomised control trials (RCT) were on infants born VPT/VLBW, of whom

only one study was on infants born ELBW. Keeping in mind that most children with developmental problems are from these populations and that the benefits of intervention might be different for infant born preterm versus full-term (Blauw-Hospers and Hadders-Algra, 2005). Hadders-Algra et al. (2017) did a systematic review of the potential effect of early intervention in infants at very high risk of CP specifically. They concluded that the literature on early intervention does not have sufficient methodological quality and provides weak evidence of an effect.

Intervention to treat non-CP motor problems

Whereas a large part of the literature assesses the effect of early developmental intervention on prevention of motor problems, with for instance 10 out of 25 interventions starting when the infant was still an inpatient in the Cochrane review from Spittle et al. (2015), several studies have also focused on interventions to improve motor performance of children already diagnosed with CP or non-CP motor problems. These studies show more beneficial results associated with intervention.

In a systematic review and meta-analysis, Smits-Engelsman et al. (2013) investigated the efficacy of various interventions on motor performance in children with DCD or motor impairment. They examined 26 studies (including one systematic review, one meta-analysis and 24 primary studies) published between 1995 and 2011 and categorised them in four types: i) task-oriented intervention; ii) traditional occupational therapy or physical therapy; iii) process-oriented intervention; and iv) chemical supplements. A task-oriented intervention aimed at learning specific motor skills that were particularly difficult for the child, whereas the process-oriented intervention focused on more global functions such as sensory integration, visual-motor perception and muscle strength. Twenty-two of the 24 primary studies showed efficacy in improving motor performance, with task-oriented interventions yielding to the strongest effects. Occupational or physical therapy also showed strong effects, whereas the effects of process-oriented intervention was weak and thus not recommended for improving motor performance in children with DCD. The evidence for chemical supplements was insufficient for a recommendation. An important limitation was that only seven out of the 24 studies used a research design producing solid evidence (Smits-Engelsman et al., 2013).

In a systematic review to determine the most effective intervention regarding QoL outcomes in children with DCD between group-based and individual-based intervention; authors found that the difference in effectiveness between intervention types was unclear,

but reassuringly, improvement of QoL was found for both (de Hóra et al., 2019). Looking specifically at task-oriented interventions among children with DCD, a recent Cochrane review by Miyahara et al. (2017) including 15 (quasi) RCTs found more inconsistent results with six studies in favour of task-oriented interventions for improved motor performance compared to no intervention, while the other studies founding no effect. However, it was impossible to perform any subgroup analysis on age, sex, severity of DCD, and intervention intensity due to the limited number of studies with complete and consistent data.

Intervention to treat CP motor problems

Several reviews have been conducted on different types of interventions to improve motor skills of children with CP. The systematic review from Dewar et al. (2015) for instance, analysed 45 studies reporting 13 exercise interventions to improve postural control in children with CP. They found five interventions with a moderate level of evidence such as gross motor task training or treadmill training with no body weight support. However, other interventions had weak or conflicting evidence. With a systematic review and meta-analysis of 41 studies including 11 RCTs, Booth et al. (2018) concluded with strong evidence that functional gait training, used to improve postural stability during walking and ability to perform multiple motor tasks while walking, results in clinically important benefits on walking speed for children and young adults with CP. However, not all interventions are effective. Novak et al. (2013) tried to synthesised all these results by doing a systematic review of interventions for children with CP. They analysed 166 articles across 64 discrete interventions seeking 131 outcomes. Evidence supported 15 interventions but most evidence for the other interventions was of low quality.

In a systematic review on the effectiveness of paediatric occupational therapy for children with disabilities, Novak and Honan (2019) analysed 129 articles including 75 systematic reviews and 54 RCTs, measuring the effectiveness of 52 interventions across 22 diagnoses and enabling analysis of 135 intervention indications. Out of these 135 intervention indications, 38 were for children with CP and nine were for children with DCD. Forty interventions (out of these 135) were supported by evidence including, for instance, bimanual training for children with hemiplegic CP, constraint-induced movement therapy for children with CP to improve hand function.

2.4.2. Follow-up for extremely preterm children

EPT children are a clearly identifiable high-risk group destined for whom structured and specialised follow-up programmes are warranted (Doyle et al., 2014) for at least two reasons: i) families want to know if their child is healthy and growing and developing normally, or if health or developmental problems are likely to be encountered in the future; ii) it is possible to improve or prevent some problems if they are detected early. For these reasons, the European Foundation for the Care of Newborn Infants (2018) recommends the assessment of the motor development in the first years for infants born EPT/VPT. The American Academy of Pediatrics recommends follow-up of VLBW infants with a structured age-appropriate neuromotor examination recommended at least once during the first and second six months of life, and each year up to five years of age (Wang et al., 2006). In addition to the control of motor development, recent guidelines for the follow-up of both children born preterm and/or with CP highlighted the importance of multidisciplinary teams in developmental surveillance (National Institute for Health and Care Excellence, 2017a, 2017b). Indeed, additional findings suggest that children with DCD could also benefit from therapeutic support addressing psychosocial and emotional challenges that arise from the condition (Haute Autorité de Santé, 2020; Karras et al., 2019).

Despite these recommendations, there is sparse information in the literature on how EPT children with developmental motor problems are followed by health care professionals. In the EPICE-SHIPS cohort, Seppänen et al. (2022b, 2022a, 2019) looked at how children born VPT are followed by health care professionals in Europe but these studies did not take into consideration the motor status of the child. Furthermore, as reported in the literature, DCD may be underrecognized by health care professionals (Blank et al., 2012; Harris et al., 2015). Based on an online survey of almost 600 physicians from Canada, the United States and the United Kingdom, Wilson et al. (2013) found that only 41% of paediatricians and 23% of general practitioners had knowledge of DCD, with around half of them (23% of the paediatricians and 9% of the general practitioners, respectively) having ever diagnosed DCD. Thus it is recommended to refer EPT children with motor difficulties to an occupational or physical therapist (Harris et al., 2015). Given the evidence for benefits of intervention for children with motor problems, investigating health service use for EPT children is a research priority.

Chapter 3 – Methods

This chapter provides a summary of the design of the EPICE-SHIPS cohort, how the data were collected and harmonised and the analytic approaches used for this doctoral project. Specific methods for the studies making up this thesis are presented in each article (chapters 4 to 7).

3.1. Data sources

3.1.1. Study design

For all the studies in this thesis, we used data from a sub-sample (restricted to children born EPT; explanation detailed below) of the SHIPS study which followed-up the EPICE cohort. The EPICE and SHIPS projects aim to provide knowledge about the use of evidence-based health care, follow-up screening and prevention programmes on health and development of VPT infants (Zeitlin et al., 2020a). The EPICE cohort is a population-based, prospective cohort of births (including stillbirths and terminations of pregnancy) between 22 weeks + 0 days and 31 weeks + 6 day of GA occurring in all maternity units in 19 regions in 11 European countries: Belgium (Flanders); Denmark (Eastern Region); Estonia (entire country); France (Burgundy, Ile-de-France and the Northern region); Germany (Hesse and Saarland); Italy (Emilia-Romagna, Lazio and Marche); the Netherlands (Central and Eastern region), Poland (Wielkopolska); Portugal (Lisbon and Northern region); Sweden (greater Stockholm) and the United Kingdom (East Midlands, Northern, and Yorkshire & the Humber regions) (Figure 4). Inclusions took place over a twelve-month period between April 2011 to September 2012, except for regions in France where they occurred over a six-month period only. The regions were selected based on their geographic and organisational diversity, as well as resources for implementing the study protocol.



Figure 4. Maps of countries and regions included in the EPICE-SHIPS cohort.

Regions included in the EPICE-SHIPS cohort: Flanders in Belgium; the Eastern Region of Denmark; Estonia (entire country); Burgundy, Ile-de-France and the Northern regions in France; Hesse and Saarland in Germany; Emilia-Romagna, Lazio and Marche regions in Italy; the Central and Eastern regions of the Netherlands; Wielkopolska in Poland; the Lisbon and Northern regions of Portugal; the East Midlands, Northern and Yorkshire and Humber regions in the United Kingdom; and the Stockholm region in Sweden.

Source: EPICE-SHIPS map.

Available at <https://www.epiceproject.eu/en/region.html> [Accessed on 19 September 2022]

3.1.2. Data collection

Perinatal and neonatal data were collected from obstetrical and neonatal records during the neonatal hospitalisation by medical staff or trained investigators using pretested standardised questionnaires with common definitions based on a previous study (Zeitlin et al., 2008). At two years of corrected age (in 2013-2014) and five years of chronological age (in 2016-2017), parents filled in questionnaires (postal questionnaires with the option of an online questionnaire at five years) on their child's development, health, use of health care services, and on the family and social context. The questionnaires were developed in English and translated into national languages, back-translated and pretested by the country teams. The five-year questionnaire was piloted with parents recruited through the EFCNI and translated versions were pretested by parents with children aged five years. In addition, as part of the five-year follow-up, children born EPT (and not those born between 28 weeks + 0 days and 31 weeks + 6 days of GA) were invited for a clinical assessment evaluating neurocognitive and motor functioning. These assessments took place in the hospital or other healthcare settings or at school (the United Kingdom regions only). An option for assessment at home was also offered in some regions. Because non-CP motor problems were identified based on this clinical assessment, our study population was restricted to children born EPT only.

Variations to the EPICE-SHIPS protocol in the French regions

In France, the EPICE-SHIPS study was carried out in tandem with the EPIPAGE-2 study, a national study of VPT births (Ancel et al., 2014). Twenty-one metropolitan regions and all overseas regions participated in EPIPAGE-2. Three regions also participated in the EPICE-SHIPS cohort: Burgundy, Ile-de-France and the Northern region, for a total of 997 inclusions <28 weeks' GA and 268 infants alive at discharge. In addition to the follow-up at two and five years of age, EPIPAGE-2's children were followed by parental questionnaire at one year. At two years, most of them had a medical visit with information on their health and development. The EPICE-SHIPS and EPIPAGE-2 questionnaires were developed conjointly to make sure that questions were harmonised to the greatest extent possible, but some EPICE-SHIPS data items could not be included or collected in exactly the same way.

3.1.3. Study population

During the study period, 4,395 EPT infants (out of 10,329 VPT infants) were included in the EPICE-SHIPS study. After exclusion of termination of pregnancy (n=702), the study included 3,693 EPT births of whom 1,671 survived to discharge (**Figure 5**); with a percentage of infants surviving to discharge after live birth ranging from 26.9% in France to 61.5% in Estonia. Among the 1,656 children who survived to two years of corrected age, 1,119 (67.6%) were followed in the two-year follow-up. At five years of chronological age, 1,021 out of the 1,654 survivors (61.7%) were followed: 850 by both parental questionnaire and clinical assessment, 52 by clinical assessment only and 119 by parental questionnaire only. In all situations, follow-up rates differed widely across regions and countries. For instance, among children followed at five years of age, who are the study population in this doctoral work, follow-up rates ranged from 38.7% (the United Kingdom) to 100.0% (Estonia).

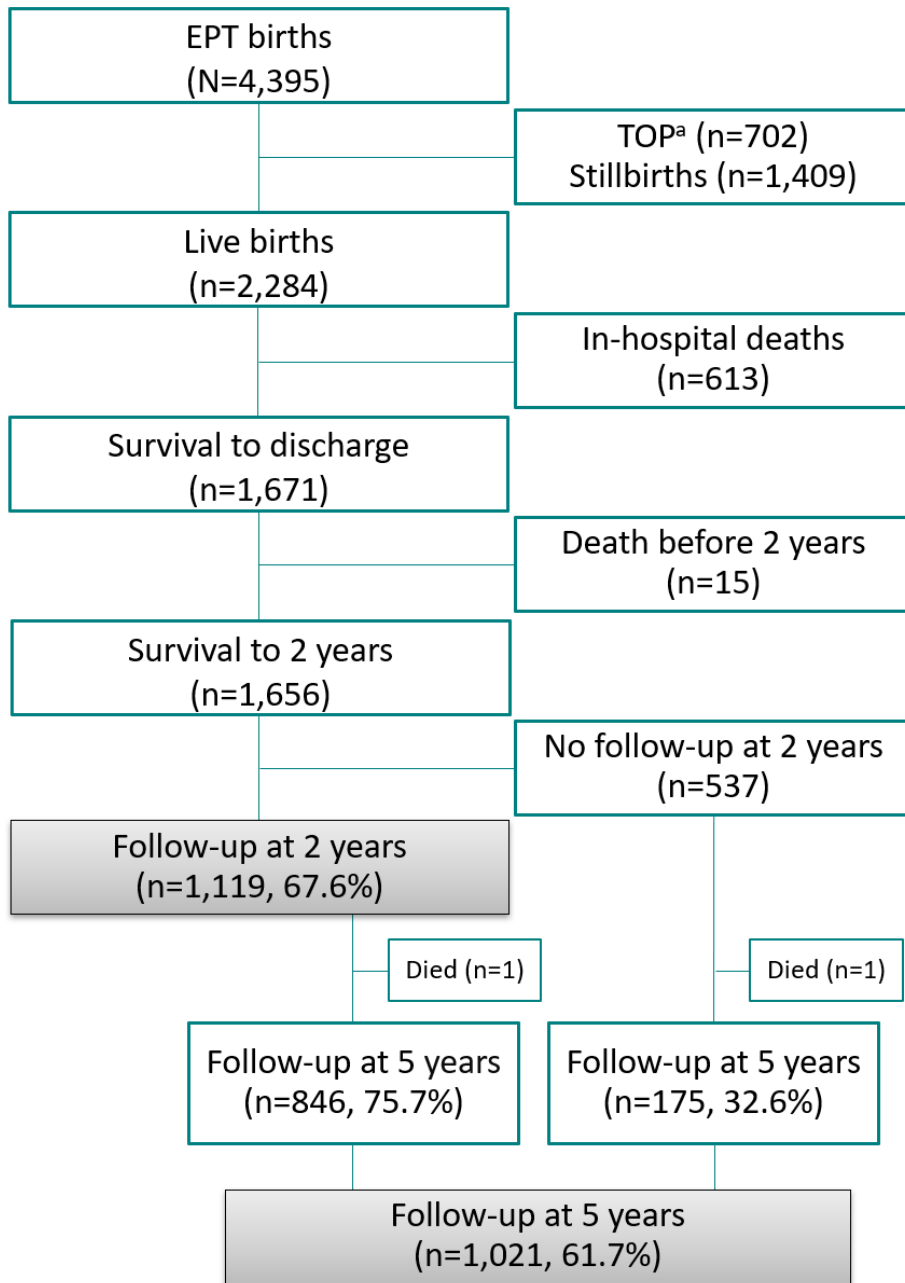


Figure 5. Follow-up of children born extremely preterm in the EPICE-SHIPS cohort.

^aTOP, Termination of pregnancy.

3.1.4. Participants included in the analyses

The MABC-2 was part of the neurodevelopmental assessment at five years of age, and thus carried out only on children born EPT. Out of 1,654 EPT infants alive at five years (**Figure 6**), 1,021 were followed-up (61.7%). Among children without CP, we excluded children with a severe NDI (n=29), defined as having an IQ <55 (<-3 SD), deafness or difficulties hearing even with hearing aids or implants or blindness or seeing light only, as their impairments can impact performance on the MABC-2 which was not designed to assess movement abilities among those children (Henderson et al., 2007). We also excluded children with missing MABC-2 data (n=116): 87 children were assessed by parental questionnaire only, whereas in 29 the MABC-2 test was incomplete or missing and imputation was not possible (see imputation process *section 3.2.1*). Except for study 1 in *chapter 4* where we excluded children with CP, the study population included both CP and non-CP groups.

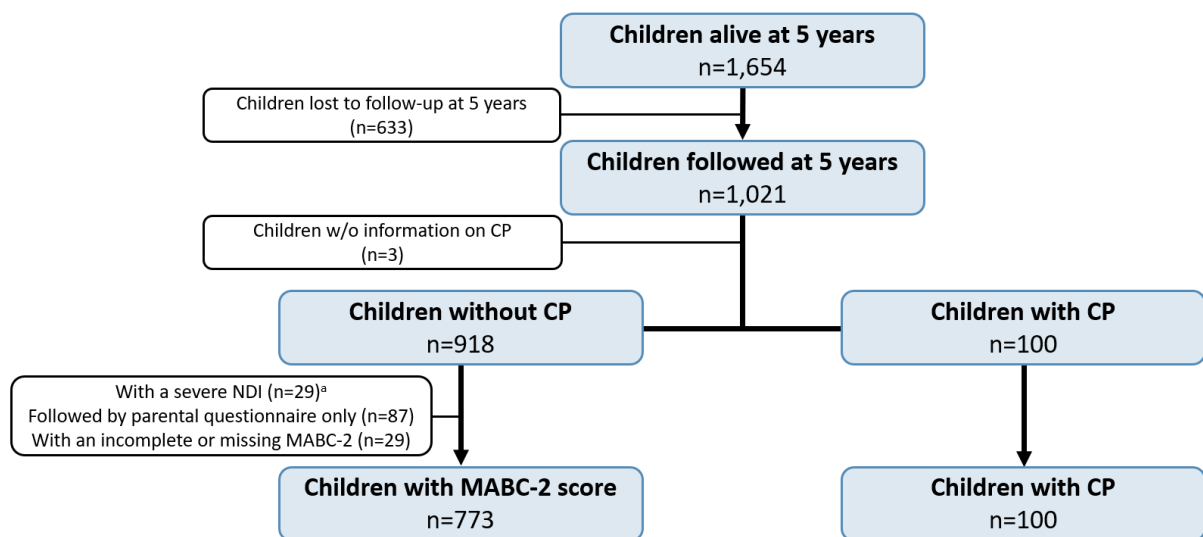


Figure 6. Flowchart of the sample selection from the EPICE-SHIPS cohort for the different analyses (children born <28 gestational weeks and followed-up at five years of age). CP, Cerebral palsy. MABC-2, Movement Assessment Battery for Children – 2nd Edition. NDI, Neurodevelopmental impairment. w/o, without.

^aDefined as an IQ <55 (<-3 SD) or severe hearing or visual impairment.

3.1.5. Consent, permissions and funding

All study regions obtained ethical approvals according to national legislations before the collection of any data for the EPICE and the SHIPS studies. The EPICE and SHIPS European studies were approved by the French Advisory Committee on Use of Health Data in Medical Research (CCTIRS) and the French National Commission for Data Protection and Liberties (CNIL). Consent was obtained from parents for the follow-up of the EPICE cohort. Parental consent was also obtained at the time of follow-up at five years for participating in the SHIPS project, according to local ethics authorisations.

Both projects were funded by the European Union: Seventh Framework Programme (FP7/2007-2013) under grant agreement No 259882 (EPICE); and Horizon 2020 Research and Innovation Program under grant agreement No 633724 (SHIPS). Continued funding was provided for analyses in the RECAP Preterm project (No 733280). Additional funding is acknowledged from the following regions: France (French Institute of Public Health Research/Institute of Public Health and its partners the French Health Ministry, the National Institute of Health and Medical Research, the National Institute of Cancer and the National Solidarity Fund for Autonomy; grant ANR-11-EQPX-0038 from the National Research Agency through the French Equipex Program of Investments in the Future and the PremUp Foundation); the United Kingdom (funding for The Neonatal Survey from Neonatal Networks for East Midlands and Yorkshire and the Humber regions).

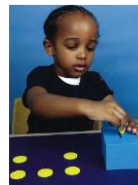
The funders/sponsors did not participate in the work.

3.2. Assessment of developmental motor problems

3.2.1. Movement difficulties using the Movement Assessment Battery for Children – 2nd Edition

The MABC-2 (Henderson et al., 2007), is a validated test to evaluate MD of children and adolescents 3 through 16 years of age by age category (Blank et al., 2019; de Kieviet et al., 2009) even in high-risk populations of EPT children (Dewey et al., 2011). It is one of the most commonly used instruments to evaluate motor problems in children (Blank et al., 2019; Costa et al., 2020; Smits-Engelsman et al., 2015) and assesses performances on eight different motor tasks from three components for all age bands. Between three and six years of age (included), children are tested on:

- manual dexterity through three tasks (posting coins with preferred and non-preferred hand, threading beads, and drawing trail);



- aiming and catching skills through two tasks (catching beanbag and throwing beanbag onto mat);



- balance skills through three tasks (one-leg balance with best and other leg, walking heels raised, and jumping on mats).



Scores from all tests are summed (with a higher score indicating better performance) and converted to an age adjusted standard or percentile scale based on the United Kingdom norms which allow the classification of motor status into three categories, within each domain and globally (Henderson et al., 2007):

- no MD (MABC-2 score >15th percentile),
- at risk for MD (MABC-2 score between the 6th and the 15th percentile),
- significant MD (MABC-2 score ≤5th percentile).

As explained in the MABC-2 manual, the 16th percentile were used instead of the 15th percentile to separate the categories “no MD” and “at risk for MD” (Henderson et al., 2007).

The MABC-2 checklist sometimes used to obtain parents' or teachers' views on a child's movement in everyday settings, was not assessed.

Administration of the Movement Assessment Battery for Children – 2nd Edition

Following the manual (Henderson et al., 2007), the assessment unfolds in three steps: i) the assessor shows and explains the test-item; ii) the child practices; iii) the child is tested and the best value is kept. The test then continues with the next test-item. Usually it takes between 20 and 40 minutes to complete all the different test-items.

In SHIPS, the MABC-2 were administered by trained psychologists or physiotherapists. Assessments were carried out by staff in local routine follow-up programmes where available (Belgium, the Netherlands, Sweden) or by the SHIPS research team (Denmark, Estonia, France, Germany, Italy, Poland, Portugal, the United Kingdom) in outpatient clinics, or at the child's home or at school when an assessment at the clinic was impossible. While it was not possible to carry out inter-rater reliability across countries, common data collection guidelines and a core data collection form were developed to standardise procedures and to ensure consistent reporting of the assessment results. Training sessions were held locally and an online discussion forum was set up to discuss possible problems emerging during the data collection.

Using norms from the United Kingdom for all countries

Out of the 11 countries included in the EPICE-SHIPS cohort, national norms exist only in Belgium, France, Italy, the Netherlands and the United Kingdom (Biancotto et al., 2013; Henderson et al., 2007; Marquet-Doléac et al., 2016; Smits-Engelsman, 2010). In a study on the Portuguese SHIPS sample applying these different norms, Costa et al. (2020) found that they had a substantial impact on the classification of motor function. This study also compared methods used for norming the MABC in each country and revealed substantial methodological heterogeneity in sample selection, size and years of the studies. For these reasons and given that not all country had local norms, we decided to uniformly apply the United Kingdom norms. These were the norms developed for the original test and are the most commonly used in the literature (Costa et al., 2020; Henderson et al., 2007). However, in our first study of risk factors the final models were re-run in a sensitivity analysis to assess how the use of local norms, in those countries where they were available, would change conclusions. We found that the use of different norms affected the country fixed effect, but not the associations between the risk factors and MD (*Supplemental material – Chapter 4*).

***Imputation of missing or incomplete Movement Assessment Battery for Children
– 2nd Edition***

Children who had missing or incomplete MABC-2 data were reviewed on a case-by-case basis by neurodevelopmental specialists and an epidemiologist (Ulrika Ådén, Raquel Costa, Samantha Johnson, Jennifer Zeitlin). If a child was unable to complete a test-item or component because of severe motor impairment, the lowest score was assigned for that test-item and/or component (n=7). This process is recommended because excluding these children will underestimate the prevalence of motor impairments.

If data were missing for a test-item/component score in the absence of other developmental problems, the average of the other test-items within the component/the average of the other components was used for imputation (n=11). Eleven Belgian children were assessed using the MABC (1st Edition) (Henderson and Sugden, 1992), but their percentile score allowed the same classification of motor status by domain and globally. In all other cases, scores were left as missing.

3.2.2. Cerebral palsy using parental report of a clinical diagnosis

Information on CP was collected in the five-year parental questionnaires; parents were asked to report any formal clinical diagnosis of CP, using the question “*Has your child been given a diagnosis of cerebral palsy by a doctor or other health professional? Yes, No.*” Parents were also asked whether their child had a CP diagnosis in the two-year questionnaire. While CP diagnoses are less reliable before five years of age, especially for those with milder symptomatology and there are more false diagnoses before this age (Hafström et al., 2018; Smithers-Sheedy et al., 2014; Surveillance of Cerebral Palsy in Europe, 2000), we compared this information for those children who were followed-up at both time points. In cases where CP status was discordant, we examined the discrepancies on a case-by-case basis using other information on the child’s health and development from the questionnaires and/or going back to local research teams for unclear cases which were resolved (seven cases considered in error at five years).

In France, CP was mostly recorded during a medical examination at five years of age (only 9.5% of children followed by parental questionnaire) and reported according to the diagnostic criteria of the Surveillance of Cerebral Palsy in Europe network (Surveillance of Cerebral Palsy in Europe, 2000), and graded using the GMFCS classification system (Ghassabian et al., 2016; Pierrat et al., 2021).

Because information on the type and severity of the CP was available in France only, CP was coded as a dichotomized variable (Yes, No) for all countries.

3.2.3. Terminology used in the manuscript to define non-cerebral palsy developmental motor problems

Contrary to CP, non-CP developmental motor problems, or “motor deficits in coordination, balance, gross and fine motor control, and visual motor integration”(Spittle and Orton, 2014), are less consensually defined and different terms are used to delineate this range of problems: DCD in the revised Diagnostic and Statistical Manual of Mental Disorders (DSM) [DSM-V] (American Psychiatric Association, 2013), Specific Developmental Disorder of Motor Function in the 10th revision of the International Classification of Diseases (ICD) [ICD-10] (World Health Organization, 1992) (renamed developmental motor coordination disorder very recently in the 11th revision of the ICD [ICD-11] (World Health Organization, 2022), non-CP motor impairment (Spittle et al., 2011), simple or complex minor neurological dysfunction (Ferrari et al., 2012), MD (Henderson et al., 2007), etc.

DCD replaced what was for a long time called the “clumsy child syndrome” or “non-CP motor perception dysfunction” (Ferrari et al., 2012). It was introduced by the American Psychiatric Association under the 1987 revision of the DSM-III-R classification system (Gueze et al., 2001), and was adopted as an international definition (Blank et al., 2019; Gueze et al., 2001). The last Edition DSM-V defined DCD by the following four criteria: i) acquiring and execution of coordinated motor skills is far below expected level for age, given opportunity for skill learning; ii) motor skill difficulties significantly interfere with activities of daily living and impact academic/school productivity, prevocational and vocational activities, leisure and play; iii) onset is in the early developmental period; and iv) motor skill difficulties are not better explained by intellectual delay, visual impairment, or other neurological conditions that affect movement (American Psychiatric Association, 2013; Blank et al., 2019). In contrast to the previous DSM Edition [DSM-IV-TR], DCD was included within the category of “neurodevelopmental disorders” and subcategorized as a “motor disorder” instead of being under the broad category of “learning disorders” (Harris et al., 2015). Furthermore, the additional criterion that the onset of symptoms occurs during the developmental period was included (Harris et al., 2015).

However, the term DCD is used by many studies to describe children with significant motor difficulties based only on the MABC-2 or similar tools assessing motor abilities without

applying the full set of criteria related to activities of daily living and other neurological conditions (Blank et al., 2019; Evensen et al., 2020; Linsell et al., 2016; Smits-Engelsman et al., 2015; Spittle et al., 2011; Spittle and Orton, 2014; Venetsanou et al., 2011). Ultimately, there is a broader debate about whether children born preterm should be diagnosed with DCD, given that the DSM-V criteria for DCD specifically excludes children with neurological disorders (beyond CP) that could explain their motor deficit (criterion iv) (American Psychiatric Association, 2013; Majnemer, 2007; Zwicker et al., 2012). In addition, using DCD as an outcome is not suited to our research which aims to elucidate relationships that are already integrated into the DCD definition, namely whether there is neurological involvement in non-CP motor problems and how it interferes with activities of daily life. For these reasons, we use the term MD, based on the MABC assessment of motor function, as done in the MABC-2 manual (Henderson et al., 2007), to define developmental motor problems among children without CP.

3.3. Assessment of the motor-related health care services

In the five-year questionnaire, parents were asked to indicate the total number of visits over the last year to specific health care providers from a pre-established, pre-tested list adapted to each country (*“How many times has your child seen these professionals or used these services over the last year? This includes appointments both at the health care office and at home.”*) (Seppänen et al., 2022b). A previous PhD thesis on health service use in the SHIPS cohort harmonised and classified these providers (Seppänen, 2020). Briefly, for each service proposed in the questionnaire, translations and back-translations were made and compared across country investigators to verify that each service was appropriately classified and comparable. For instance, “motor development specialist” in Estonia, “physical therapist” in Poland, and “psychomotor therapist” in France correspond to the same overall classification of “physiotherapist or motor development therapist.” In addition, free-text answers, possible after the listing of the different professionals or services, were also translated and recoded into existing categories or new services. Meaningful groups of services were created after discussing and comparing the data within the consortium. Given our specific interest in motor developmental problems, we grouped together children who had received MRHC services, defined as at least one visit to any of the following health professionals: (1) physiotherapist, motor development or psychomotor therapist, or kinesiologist; (2) occupational therapist; or

(3) early intervention specialist. Other health care services were also examined and this information is described in more detail in *chapter 6* (study 3).

3.4. Assessment of the health-related quality of life

3.4.1. The Pediatric Quality of Life Inventory™

In the five-year parental questionnaire, caregivers were asked to complete the parent-reported Pediatric Quality of Life Inventory™ (PedsQL) generic core scales (Varni et al., 2001, 1999), age version 5-7 years. This instrument measuring the child's HRQoL is a commonly-used multidimensional questionnaire (Hilliard et al., 2013a; Jardine et al., 2014; Upton et al., 2008) which has demonstrated reliability and validity in healthy school populations (Varni et al., 2003, 2001), as well as paediatric populations with acute or chronic health conditions (Varni et al., 2006; Varni and Burwinkle, 2006). It consists of 23 items for which parents use a 5-point Likert scale to answer the question: *"in the past month, how much of a problem has your child had with ..."* The items cover four domains: physical (8 items), emotional (5 items), social (5 items) and school functioning (5 items). Items are then reverse-scored and linearly transformed to a 0 to 100 scale, with higher score indicating a better HRQoL (Varni et al., 2001). Three summary scores are available: the physical health summary score (using the 8 items on physical functioning), the psychosocial health summary score (combining the 15 items on emotional, social and school functioning), and the total scale score (using all 23 items). If more than 50% of the items are missing the corresponding summary score is not computed.

3.4.2. Does the person who assesses health-related quality of life influence the values reported?

The five-year old questionnaire was filled out by the child's primary care taker and this could be the mother, father or, infrequently, another person. Mothers and fathers may have different perspectives on child health and behaviour (Upton et al., 2008). At the beginning of the five-year parental questionnaire, the respondent was asked to answer the question "What is your relationship to the child?". In the study population for the study on HRQoL (*chapter 7, study 4*) (n=810), 86.9% (n=704) of the respondents were mothers and 11.5% (n=93) were fathers. "Other relative or family member", "Other caregiver", and missing information to that question represented only 13 cases. This distribution is relatively close to the one reported by Varni et al. (2001) in a study on the validation of the PedsQL in healthy and patient paediatric populations, i.e., 80% mothers, 13% fathers and 7% other. To assess whether the respondent was a factor to be considered in our analysis, we assessed whether there were differences overall in maternal versus paternal answers to the PedsQL questionnaire. As illustrated by the quantile-quantile plot presented in [Figure 7](#), and confirmed by the Kolmogorov-Smirnov test of the equality of distributions (p-value=0.73) the responses of mothers and fathers followed a very similar distribution. We therefore did not distinguish between the respondent in our study of HRQoL.

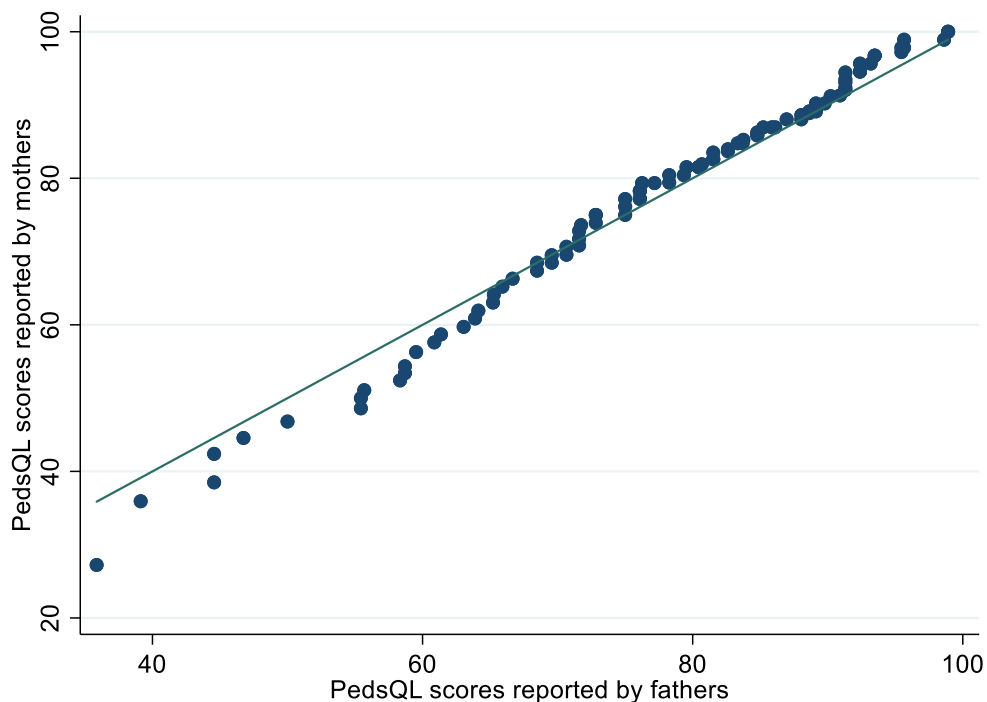


Figure 7. Quantile-quantile plot of paternal and maternal PedsQL scores in the study 4 on HRQoL.
PedsQL, Pediatric Quality of Life Inventory™.

3.4.3. Effect size – Clinically meaningful change in health-related quality of life scores

HRQoL assessments do not have clinical cut-offs indicating relevant or clinically meaningful change values (Hilliard et al., 2013a), i.e., perceived as a significant improvement or worsening of the child's well-being. In other words, small numerical differences in mean HRQoL scores might give statistically significant results when large sample sizes are used, but statistical significance is not equivalent to clinical significance (Osoba et al., 1998).

To overcome this limit and obtain a reference threshold, researchers have tried to estimate the minimal clinically important difference which is the numerical value indicating the smallest amount of HRQoL change which patients perceive as beneficial or detrimental (Crosby et al., 2003). In this context, differences of 5-10 points on a 100-point scale are regarded as clinically significant (Fayers and Machin, 2007). Specifically on PedsQL scores, Hilliard et al. (2013) established the amount of change that youth with diabetes and their parents perceive as meaningful in everyday functioning or activities around 4.5 to 6.5 points depending on age and type of diabetes. In addition, the same order of magnitude was found during the PedsQL's validation study between ill and healthy children (Varni et al., 2001).

Another useful method when measurements have no intrinsic meaning is to calculate the effect size (δ) to provide information about the magnitude of the difference between each group and the reference group with respect to the overall distribution (Sullivan and Feinn, 2012). Cohen's δ effect size is one commonly used measure which expresses the difference between two means in SD units (Cohen, 1988). Effect sizes of 0.2, 0.5, and 0.8 of the standardised mean difference are generally considered small, medium and large effect sizes, respectively.

In *chapter 7* (study 4), we used both these concepts – comparing minimally clinical effect sizes and using Cohen's δ effect size – to interpret differences in HRQoL between groups.

3.5. Risk factors and confounders

For each analysis, the selection of covariables was guided by the hypothesised relationships between the main exposure and outcome variables and based on biological plausibility and the scientific literature. Because of the range of questions in this doctoral work, some variables are treated both as risk factors and confounders. The principal variables used in the analyses and collected as part of the EPICE and SHIPS studies are listed below.

3.5.1. Perinatal and neonatal characteristics

Perinatal factors (defined as those related to the pregnancy and the birth) were GA (≤ 24 ; 25; 26; 27 completed weeks) (defined as the best estimate determined by the obstetrical team based on information for last menstrual period and antenatal ultrasounds), small for GA (SGA) ($< 3^{\text{rd}}$; 3-9th; $\geq 10^{\text{th}}$ percentile) (Zeitlin et al., 2017), Apgar score < 7 at five minutes (no; yes), sex (female; male), multiple birth (singleton; multiple), delivery in maternity level 3 (no; yes), antepartum haemorrhage after week 20 (no; yes), PROM > 12 hours (no; yes), preeclampsia/eclampsia/HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome (no; yes), any antenatal corticosteroids (no; yes), and congenital anomaly (no; yes) (Draper et al., 2017).

Neonatal factors included IVH grade determined using Papile's classification (Papile et al., 1978) (Grade I/II – Bleeding occurs just in the germinal matrix (Grade I) or occurs also inside the ventricles (Grade II); Grade III – Blood in lateral ventricle with ventricular dilatation; Grade IV – Parenchymal involvement), cPVL (recorded if cystic abnormalities were present on ultrasound or CT scan) (no; yes), ROP stage III or more (no; yes), surgical NEC (requiring surgery or peritoneal drainage) (no; yes), presence of BPD (defined as supplemental oxygen and/or ventilatory support [CPAP or mechanical ventilation] at 36 weeks' postmenstrual age) (no; yes), receipt of postnatal corticosteroids (Nuytten et al., 2017), presence of confirmed late infection > 72 hours of life (no; yes), and breastfeeding at discharge (no; yes).

Some perinatal and neonatal factors, associated with motor impairment in the literature (Evensen et al., 2020; van Hoorn et al., 2021; van Lieshout et al., 2017; Linsell et al., 2016), could not be included because information was not systematically collected (intrauterine infection, chorioamnionitis), samples were small (e.g., study 2 – magnesium sulfate administered in only 36 cases) or variables were collinear (mechanical ventilation and BPD). Finally, wide variations in medical practices between the participating countries

(e.g., caesarean section) (Wolf et al., 2021) complicated the interpretation of some interventions.

3.5.2. Sociodemographic characteristics

Sociodemographic factors included maternal age at childbirth (≤ 24 ; 25-34; ≥ 35 years), parental cohabiting status (married/couple/cohabiting; single/other), maternal educational level [adapted from the International Standard Classification of Education (ISCED) – 2011 levels] (UNESCO Institute for Statistics, 2012), (\leq lower secondary (ISCED 0-2); Upper secondary, post-secondary non-tertiary or short-tertiary (ISCED 3-5); \geq bachelor (ISCED 6-8), household unemployment status (employed or other situation [including student, parental leave, home parent and other]; at least one parent unemployed), parity (primiparous, multiparous), and maternal country of birth (native-born; other European country; non-European country).

Due to the high correlation between parity (number of mother's previous births) and the number of siblings, we had to choose one and decided to use parity which is more commonly collected and easier to interpret. Multiple mechanisms underlie the effect of having siblings as a covariate such as stimulation, which may differ if the sibling is younger or older, parental time available, family dynamics related to step-siblings, etc. The number of siblings is also highly correlated with multiple pregnancies, a variable necessary to fully consider the perinatal situation. Finally, the number of siblings reflects decisions after the EPT child's birth and may be related to their health status. The effect of siblings on a the child's development has been found to vary widely – perhaps reflecting these multiple situations – being supportive or highly detrimental for mental health (Doyle et al., 2014; Wolke and Skew, 2012). Furthermore, parity, especially among mother with advanced age (≥ 35 years) is highly related to maternal and neonatal outcomes (Schimmel et al., 2015).

3.5.3. Developmental characteristics

In the analyses, other developmental impairments, frequent in this population, were used to select appropriate study populations, as adjustment variables and for sub-group analyses. Several variables were constructed to describe these developmental impairments.

Neurodevelopmental impairments

NDI integrates cognitive, hearing and visual impairment, all three with definition and harmonisation details presented in [Table 1](#). Cognitive abilities were assessed using the Wechsler Preschool and Primary Scale of Intelligence – Revised, Third or Fourth Edition (WPPSI-R/III/IV) depending on the country (Wechsler, 2012, 2002, 1989). The WPPSI-IV was preferred, but when it was not locally normed and other editions were normed, these were used (i.e., WPPSI-R in Portugal, and WPPSI-III in Belgium, Germany, Italy and the Netherlands). Full-scale IQ was calculated using local norms and impairment categories were defined according to the mean SD: IQ score ≥ 85 (≥ -1 SD) as normal range; IQ score between 70 and 84 (< -1 SD; -2 SD) as mild impairment; IQ score between 55 and 69 (< -2 SD; -3 SD) as moderate impairment; and IQ score ≤ 54 (< -3 SD) as severe impairment.

	None	Mild	Moderate	Severe
Cognition				
Clinical assessment	IQ scores ≥ -1 SD (scores ≥ 85)	IQ scores -1 SD to -2 SD (scores 70 to 84)	IQ scores -2 SD to -3 SD (scores 55 to 69)	IQ scores < -3 SD (scores ≤ 54)
Hearing				
Parental report	Q: Does your child have any difficulties hearing? A: No difficulties hearing	Q: Does your child have any difficulties hearing? A: Some difficulties hearing but does not require hearing aids or implants	Q: Does your child have any difficulties hearing? A: Needs hearing aids or implant but hears well with them	Q: Does your child have any difficulties hearing? A: My child is deaf OR A: Has difficulty hearing even with hearing aid or implant
French variation: <i>medical report (and parental report if missing)</i>	No hearing loss	Hearing loss ≤ 40db OR Hearing loss corrected with hearing aid (not depending on initial loss)	40db $<$ Hearing loss ≤ 70db not corrected or partially corrected with hearing aid (unilateral or bilateral)	Hearing loss > 70db not corrected or partially corrected with hearing aid (unilateral or bilateral)
Vision				
Parental report	Q: Does your child have any difficulties with his or her vision? A: No difficulties with vision	Q: Does your child have any difficulties with his or her vision? A: Needs to wear glasses but sees well when wearing them	Q: Does your child have any difficulties with his or her vision? A: Has difficulties seeing even wearing glasses	Q: Does your child have any difficulties with his or her vision? A: Blind or sees light only
French variation: <i>medical report (and parental report if missing)</i>	Distance visual acuity (Sander-Zanlonghi scale): Binocular visual acuity $\geq 5/10$	Distance visual acuity (Sander-Zanlonghi scale): $3.2/10 \leq$ Binocular visual acuity $< 5/10$	Distance visual acuity (Sander-Zanlonghi scale): $1/10 \leq$ Binocular visual acuity $< 3.2/10$	Distance visual acuity (Sander-Zanlonghi scale): Blindness or Binocular visual acuity $< 1/10$

Table 1. Classification of neurodevelopmental impairment in each developmental domain at five years of age in the EPICE-SHIPS cohort.

For all countries and all developmental domains, consistent comments noted by an examiner or the research team can surpass some variables and justify a classification of impairment.

IQ, Intelligence quotient. SD, Standard deviation. Q, Question. A, Answer (item possibilities). Db, Decibel.

As explained in *section 3.1.4*, children with a severe NDI were excluded from all analyses of the MABC-2 as it was not designed to assess movement abilities among these children (Henderson et al., 2007). In study 3 (*chapter 6*), cognitive impairment was analysed separately as a developmental problem potentially associated with receiving specialised health care services, including MRHC. In study 4 (*chapter 7*), we did a secondary analysis excluding children with a moderate to severe NDI because these impairments could impact directly the HRQoL (Gire et al., 2019; Natalucci et al., 2017; Saigal et al., 2016; Vieira and Linhares, 2016).

Behavioural problems

Behavioural problems are common sequelae of EPT birth. As part of the five-year parental questionnaire, parents filled in the SDQ which is a well-validated and widely used screening questionnaire to assess children's behavioural and emotional difficulties (Croft et al., 2015; Goodman, 2001, 1997; Vogels et al., 2009). It evaluates 25 items over the previous six months with a 3-point Likert scale ("Not true"; "Somewhat true"; "Certainly true") and provides five subscale scores: emotional symptoms, peer relationship problems, conduct problems, hyperactivity/inattention, prosocial behaviour. Subscale scores can be combined in scores on internalizing problems (emotional symptoms and peer relationship problems), externalizing problems (conduct problems and hyperactivity/inattention), and a total score (combining internalizing and externalizing problems). The prosocial behavioural score is analysed on its own and not included in the other combined scores. The scores are categorised as "normal", "borderline", or "abnormal" (Goodman, 2001, 1997).

In study 3 (*chapter 6*), behavioural difficulties were analysed separately as a developmental problem potentially associated with receiving specialised health care services, including MRHC. Indeed, we hypothesised that children with MD and behavioural difficulties may be more likely to be detected by health care professionals and receive health services. In study 4 (*chapter 7*), we considered excluding children with abnormal scores on the SDQ in a secondary analysis to focus on the association of MD on HRQoL in the absence of other developmental problems, as described above. However in comparing the items of the PedsQL and SDQ questionnaires, we observed that several of them measure similar constructs: e.g., "Having aches or pains" (PedsQL – Physical functioning) and "Often complains of headaches, stomach-aches or sickness" (SDQ); "Feeling afraid or scared" (PedsQL – Emotional functioning) and "Many fears, easily scared" (SDQ); "Feeling sad" (PedsQL – Emotional functioning) and "Often unhappy, down-hearted or tearful" (SDQ); "Worrying about what will happen to him

or her” (PedsQL – Emotional functioning) and “Many worries, often seems worried” (SDQ); “Getting along with other children” (PedsQL – Social functioning) and “Generally liked by other children” (SDQ); “Paying attention in class” (PedsQL – School functioning) and “Easily distracted, concentration wanders” (SDQ); etc. Last, as mentioned by Zwicker et al. (Zwicker et al., 2013) in a systematic review on QoL domains affected in children with DCD, SDQ can also be used as a measure of QoL in many studies. Given this overlap, we did not undertake this secondary analysis.

3.6. Analytic approaches

This section describes the main statistical methods used in this doctoral work. We faced multiple analytic questions in answering our research questions using the EPICE-SHIPS cohort, namely, how to manage loss to follow-up and missing data, the hierarchical structure of the data, and the left-skewed distribution of the PedsQL score and its potential impact.

3.6.1. Loss to follow-up and missing data

Inverse probability weighting to correct for potential attrition bias

With 61.7% (n=1,021) of the children born EPT followed at five years of age, the EPICE-SHIPS cohort has a substantial rate of attrition. As shown in [Table 2](#), some sociodemographic, perinatal and neonatal characteristics were associated with loss to follow-up. Children were less likely to be included in the follow-up when they had higher social risk (e.g., younger and foreign-born mothers), however, results for health risks were less clear except for SGA. We observed differences in follow-up rates between countries (from 38.7% in the United Kingdom to 100.0% in Estonia)

	Children followed at 5 years of age		Children lost to follow-up at 5 years		<i>p-value</i> ^a
	N	%	N	%	
Sociodemographic characteristics					
Maternal age at childbirth (years)					<0.001
<25	121	11.9	151	24.0	
25-34	610	60.0	353	56.2	
≥35	286	28.1	124	19.7	
<i>Missing</i>	4	0.4	5	0.8	
Parity					0.010
First child	604	59.9	335	53.7	
Second child	252	25.0	152	24.4	
Third child or more	153	15.2	137	22.0	
<i>Missing</i>	12	1.2	9	1.4	
Maternal country of birth					<0.001
Native-born	786	77.2	384	65.3	
Other European country	67	6.6	51	8.7	
Non-European country	165	16.2	153	26.0	
<i>Missing</i>	3	0.3	45	7.1	
Perinatal and neonatal characteristics					
Gestational age (completed weeks)					0.69
≤24	132	12.9	108	17.1	
25	191	18.7	111	17.5	
26	292	28.6	183	28.9	
27	406	39.8	231	36.5	
<i>Missing</i>	0	0.0	0	0.0	
Small for gestational age					0.031
<3 rd percentile	157	15.4	73	11.5	
3-9 th percentile	82	8.0	45	7.1	
≥10 th percentile	782	76.6	515	81.4	
<i>Missing</i>	0	0.0	0	0.0	
Child sex					0.83
Female	489	47.9	296	46.8	
Male	532	52.1	337	53.2	
<i>Missing</i>	0	0.0	0	0.0	
Multiple birth					0.41
Singleton	733	71.8	469	74.1	
Multiple	288	28.2	164	25.9	
<i>Missing</i>	0	0.0	0	0.0	
Congenital anomaly					0.23
No	936	91.7	583	92.1	
Yes	85	8.3	50	7.9	
<i>Missing</i>	0	0.0	0	0.0	
Severe neonatal morbidity^b					0.31
No	747	74.6	434	71.3	
Yes	255	25.4	175	28.7	
<i>Missing</i>	19	1.9	24	3.8	
Bronchopulmonary dysplasia^c					0.54
No	642	63.9	366	59.2	
Yes	362	36.1	252	40.8	
<i>Missing</i>	17	1.7	15	2.4	

Breastfeeding at discharge					<i><0.001</i>
No	447	44.7	341	56.7	
Yes	554	55.3	260	43.3	
Missing	20	2.0	32	5.1	
Global					
Followed-up at 2 years of age					<i><0.001</i>
No	175	17.1	361	57.0	
Yes	846	82.9	272	43.0	
Missing	0	0.0	0	0.0	
Country (region)					
Belgium (Flanders)	70	55.1	57	44.9	
Denmark (Eastern Region)	52	59.8	35	40.2	
Estonia (entire country)	38	100.0	0	0.0	
France (Burgundy, Ile-de-France, Northern Region)	189	71.6	75	28.4	
Germany (Hesse, Saarland)	79	42.7	106	57.3	
Italy (Emilia-Romagna, Lazio, Marche)	173	77.6	50	22.4	
The Netherlands (Central Eastern)	75	85.2	13	14.8	
Poland (Wielkopolska)	52	78.8	14	21.2	
Portugal (Lisbon, Northern Region)	113	72.4	43	27.6	
The United Kingdom (East Midlands, Northern, Yorkshire and the Humber)	138	38.7	219	61.3	
Sweden (Greater Stockholm)	42	66.7	21	33.3	

Table 2. Characteristics of children followed and lost to follow-up at five years of age.

Values are frequencies (Ns rounded to a whole number) and percentages (% excluding missing values and rounded to one decimal).

^aP-values from Wald test of logistic regressions adjusted on country and taking into consideration clustering within multiple pairs.

^bIncluded intraventricular haemorrhage grade III/IV, cystic periventricular leukomalacia, retinopathy of prematurity stage III or more, and surgical necrotizing enterocolitis.

^cDefined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.

To correct for the attrition bias in the sample resulting from this differential loss to follow-up, we used inverse probability weighting (IPW) to give more weight to children who were followed, but who have characteristics similar to those who were less likely to be followed. To do this, each child was assigned a probability of being followed up, which we estimated using data collected at baseline. The 27 variables used to estimate this probability are listed in **Table 3**: they are the main variables associated with loss to follow-up (p-value adjusted on country <0.2)) and/or the main variables potentially affecting loss to follow-up, as reported in the literature.

Perinatal/Neonatal			Sociodemographic
<ul style="list-style-type: none"> • Previous caesarean section • Antepartum haemorrhage after week 20 • Admission for preterm labor/contractions after week 20 • The mother has preeclampsia/eclampsia/HELLP • Premature rupture of membranes (>12hours) • Antenatal corticosteroids • Delivery in maternity level 3 • Mode of delivery 	<ul style="list-style-type: none"> • Gestational age • Small for gestational age • Birthweight • Apgar score <7 • Child sex • Multiple pregnancy • Hospital transfer during neonatal care • Congenital anomalies 	<ul style="list-style-type: none"> • Severe neonatal morbidity^a • Bronchopulmonary dysplasia^b • Any surgery before discharge • Use of any continuous positive airway pressure • Use of mechanical ventilation • Prophylactic surfactant in the 2 hours after birth • Breastfeeding at discharge 	<ul style="list-style-type: none"> • Maternal age at childbirth • Maternal country of birth • Maternal parity before childbirth • Country

Table 3. List of the variables included in the creation of the inverse probability weighting to correct the attrition bias.

HELLP syndrome, Haemolysis, Elevated Liver enzyme, Low Platelets syndrome.

^aIncluded intraventricular haemorrhage grade III/IV, cystic periventricular leukomalacia, retinopathy of prematurity stage III or more, and surgical necrotizing enterocolitis.

^bDefined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.

As explained by Seaman and White (2013), the missingness model should contain enough covariates to minimise bias, but with a finite sample, the addition of more and more variables will ultimately lead to a fitted probability of zero for at least one incomplete case. In our research, we tested the creation of seven different IPW by varying the number of variables retained in the models. Reassuringly, we observed relatively small differences in the resulting weights.

The distribution of IPW values ranged from 1.0 and 10.3 in the weights used for the study, and with a mean (SD) of 1.63 (0.78) (Figure 8). To be sure that these large weights did not impact our conclusions, we replicated the final analyses with IPW truncated to the 95th percentile value (3.00) and found similar results.

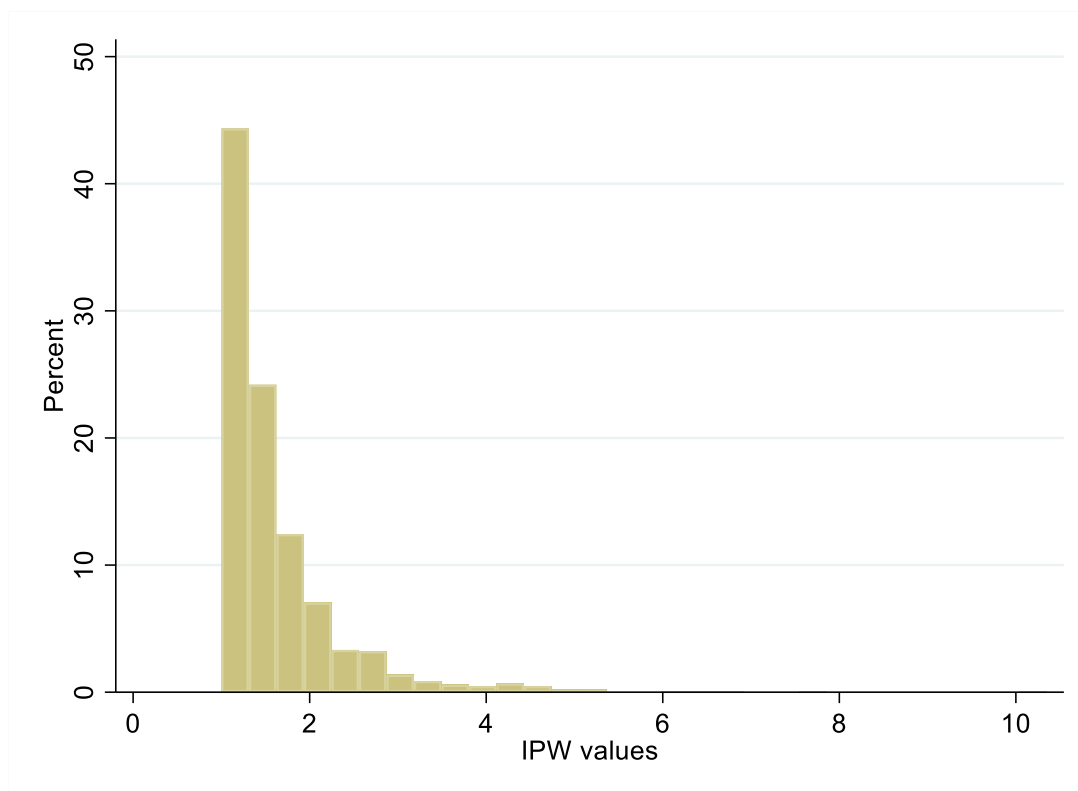


Figure 8. Distributions of the IPW values in our study sample. IPW, Inverse probability weighting.

Multiple imputation by chained equations to impute missing data

Multiple imputation by chained equations (MICE) was used both to impute missing data for covariates used to create the weights ($m=20$), and to impute missing values for covariates used in the final models of the different articles ($m=20$). The first use was necessary to have a weight available for all individuals. Percentages of missing data are detailed in each article.

With this method, twenty complete imputed datasets were generated, with the missing values replaced by imputed values from their predictive distribution based on the observed data, and analysed individually (Sterne et al., 2009). Then, results of the model parameters were pooled into a single estimate by applying Rubin’s rules which take account of the variability in results between the imputed datasets (Royston and White, 2011; White et al., 2011). As for other multiple imputation methods, the standard assumption when using MICE

is that missing values occur at random, i.e., the probability of missingness depends solely on observed data (Audigier et al., 2018). As recommended, final models used both IPW and MICE (Seaman et al., 2012). Lastly, we reran final models using unweighted and complete case samples and compared results to verify the missing at random assumption (Sterne et al., 2009), i.e., the process of missingness is fully captured by the different variables included in the MICE models (Collins et al., 2001).

We did not impute data for children with missing MABC-2 or PedsQL score as the missing at random assumptions likely did not hold, i.e., the relationships between non-response and the variables on which it occurs cannot be fully explained by observed data (Collins et al., 2001). However, we analysed the characteristics of children with and without MABC-2 scores and PedsQL scores for studies 1 and 4 and tables comparing these populations are provided as *supplemental material* for these publications.

3.6.2. Hierarchical structure of the data

The data used for our studies are clustered on at least two levels: the mother or household level, and the country level. Multiples have the same biological parents (e.g., sharing the same maternal and pregnancy risk factors) and usually live in the same household (e.g., share the same family context and living environment). In our study population, 452 out of the 1,654 children surviving to discharge (27.3%) were multiples. Furthermore, children living in the same country are potentially exposed to the same socioeconomic context, public health policies, health care system or other unmeasured societal factors. Thus, these data are clustered (or correlated) and not fully independent.

A hierarchical structure with intra-cluster correlations violates the assumption of independence in statistical models. In this context, analyses assuming independence of the observations underestimate the true variance and lead to an inflation of Type I error and the risk of obtaining false associations (Williams, 2000).

One option for analysis of hierarchical data is using random effects models; however, modelling country as random effect appeared inappropriate for two reasons: because the participating regions were not selected at random in EPICE-SHIPS, and because random effect models require at least 20-30 clusters and we had only 11 countries in EPICE-SHIPS (Maas and Hox, 2004). Thus, we modelled country as a fixed effect. To assess the impact of this choice, we replicated most of our models using a random effect for country with similar results. We

took into consideration clustering within multiple pairs by specifying a cluster for the mother/household with the use of robust variance estimators, relaxing the assumption of non-independent observations between multiples. The robust (or sandwich) estimate of variance, calculated using the Huber-White method (Huber, 1967; White, 1982), makes it possible to correct the asymptotic standard errors which are not independent and identically distributed (Maas and Hox, 2004). Since, the Huber method does not perform well when there are only a few observations by cluster, it has been adapted to cluster samples using cluster-robust standard errors (Rogers, 1994).

3.6.3. Left-skewed distribution of the Pediatric Quality of Life Inventory™ scores

Linear regression models are the most commonly used in the HRQoL literature (Ferreira et al., 2008; Micceri, 1989; Qasemi et al., 2020; Wong et al., 2019). However, as observed in several HRQoL measures, the PedsQL score deviates from the normal distribution. It has both a ceiling effect with data bounded or right censored at the maximum (here 100/100) for children rated in "full health" (16.1% (n=126), 3.6% (n=28) and 2.2% (n=17) for physical, psychosocial and total score, respectively), and a left-skewed distribution due also to some children with severe impairments (confirmed using Shapiro-Wilks and Kolmogorov-Smirnov tests) (**Figure 9**) (Ferreira et al., 2008; Micceri, 1989; Qasemi et al., 2020; Wong et al., 2019). In other words, there is a variability in PedsQL scores that is not being accounted for when children score 100 and we do not know which children have "true" scores of 100 and which ones have censored scores. Furthermore, the use of classic transformations (cubic, square, log, etc.) did not resolve the problem of ceiling effect and left-skewed distribution (results not shown).

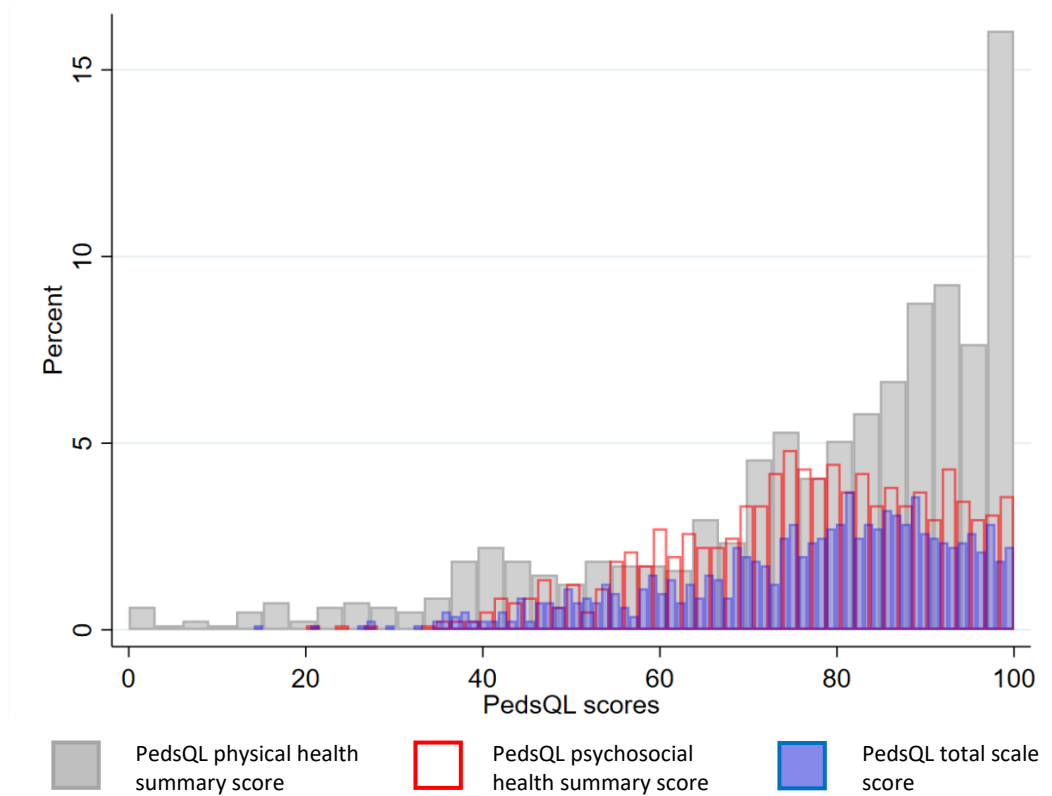


Figure 9. Distributions of the PedsQL scores in our study sample. PedsQL, Pediatric Quality of Life Inventory™.

Censored regression models

In particular, ignoring the ceiling effect might result in biased and inconsistent estimates (Wells and Hintze, 2007; Wilhelm, 2008). In addition, there is no clear criterion for how large the sample size has to be before the central limit theorem applies (Wells and Hintze, 2007). Censored regression models, namely the Tobit or the censored least absolute deviations (CLAD), make it possible to produce consistent estimates in this situation (Austin et al., 2000; Greene, 2012; Powell, 1984; Rowen et al., 2009; Sullivan and Ghushchyan, 2006). The Tobit model handles censoring by assuming the true value is a normal distribution whose mean is given by a linear combination of the covariates (Shafie et al., 2021; Wilhelm, 2008), the CLAD model assumes that the median is a linear combination of the covariates but leaves the distribution unspecified (Wilhelm, 2008). In the absence of homoscedasticity and normality, misspecification of the Tobit estimators is not automatic but the CLAD model has been shown to be more robust (Wilhelm, 2008). Because both of these models gave very similar results and to allow our results to be more comparable to other studies, we used linear models for our main analysis. However, these results were provided as supplemental material (*Supplemental material – Chapter 7*).

Quantile regression models

In the *chapter 7* (study 4), we also explored possible differential effects over the HRQoL distribution with quantile regression models (Koenker, 2005; Petscher and Logan, 2014).

By focusing on the entire conditional distribution of the dependent variable and not only the mean, quantile regression models provide a more detailed picture than classic linear regression models. Instead of allowing for an estimate of the average relation between the predictor and the outcome, quantile regression models provide estimates of the relation between the predictor and the outcome at multiple points of the outcome's distribution (Pereira et al., 2022; Petscher and Logan, 2014). In other words, it allows for the possibility that the importance of the predictor may be different depending on the quantile of the outcome (Petscher and Logan, 2014). As explained by Petscher and Logan (2014), instead of the question "What is the relation between X and Y?" analysed with linear regression, quantile regression extends this to, "For whom does the relation between X and Y exist?" as well as testing for whom the relation is stronger or weaker.

In addition, quantile regression provides another option for analysing a censored dependent variable and/or non-normally distributed data. Quantile regression is semiparametric without assumption made about the distributional form and so is not impacted by violations of the normality assumption (Petscher and Logan, 2014). This is because in quantile regression, the estimation process is repeated for any quantile the analyst is interested in, with a unique intercept, slope, and error term estimated each time.

Nonetheless, one important limit of quantile regression models is the division of the sample into two groups leading to a reduction of the statistical power. Thus, even if research on this question is limited, it is necessary to have a significant sample size within each group. Thus, the selection of the number and values of quantiles have to be considered giving thought to the sample size, the number of parameters and the distribution of the data (Cade and Noon, 2003; Petscher and Logan, 2014). In the *chapter 7* (study 4), to be sure to have enough individuals in each group, we used quantiles 10, 25, 50, 75 and 90, which are also commonly used in the literature.

We have summarized the main information of the different analytic approaches used in the four studies included in this doctoral work in [Table 4](#).

	Study 1	Study 2	Study 3	Study 4
Outcome	Non-CP MD (at risk for MD, significant MD) compared to no MD (variable in 3 classes)	CP and significant MD compared to no MD (variable in 3 classes)	Use of MRHC services (binary variable)	PedsQL scores (continuous variable)
Exposure	Sociodemographic, perinatal and neonatal risk factors		No MD At risk for MD Significant MD CP	
Covariates/adjustments	All treated as risk factors 3 models: i) Unadjusted ii) Adjusted for sociodemographic and perinatal factors iii) Additionally adjusted for neonatal factors	All treated as risk factors 4 models: i) Unadjusted ii) Adjusted for sociodemographic factors iii) Additionally adjusted for perinatal factors iv) Additionally adjusted for neonatal factors	Adjusted for MABC-2 total score	All treated as confounders 2 models: i) Adjusted for child age and sex ii) Additionally adjusted for sociodemographic factors
Exclusions	Children without MABC-2 score			
	Children with CP	Children at risk for MD	Children without information on MRHC services	Children without PedsQL score
Model used	Multinomial logistic regression		Logistic regression	Linear regression
Sub-group analyses				With the exclusion of children with a moderate to severe NDI
				Stratified on the receipt of MRHC services
Additional statistical points	Country modelled as fixed effect			
	Accounting for clustering of multiple births			Accounting for clustering of multiple births
	IPW & MICE			IPW & MICE
Sensitivity analyses	Without IPW and/or MICE		With IPW	Without IPW and/or MICE
	Using MABC-2 national norms	With the exclusion of children with a severe NDI in the CP group		With the exclusion of children with a severe NDI in the CP group
				Using Cohen's δ effect size
				Using censored regression models

Table 4. Summary of the different analytic approaches used in the four studies of this doctoral work.

CP, Cerebral palsy. IPW, Inverse probability weighting. MABC-2, Movement Assessment Battery for Children – 2nd Edition. MD, Movement difficulties. MICE, Multiple imputation by chained equations. MRHC, Motor-related health care. NDI, Neurodevelopmental impairment. PedsQL, Pediatric Quality of Life Inventory™. Gray, Not done.

Chapter 4 – Prevalence of movement difficulties in children born extremely preterm and associated risk factors

4.1. Preface

Whereas the estimation of prevalence is important for assessing how many children have non-CP MD, it is not possible to derive an accurate estimate by reading the current scientific literature. In addition, an understanding of associated risk factors makes it possible to identify at-risk children for follow-up and early intervention. However, similar uncertainty exists when reviewing the literature on risk factors for non-CP MD, with only male sex and GA being consistently reported. For these reasons, the first step of this doctoral work focused on the measurement of non-CP MD prevalence among children born EPT and the analysis of associated risk factors.

For this study we excluded CP children, as done in most studies of the MABC-2 or MD in general. This exclusion is justified because CP is a well-defined neurodevelopmental disorder with a specific definition and the associated risk factors are (at least partially) different with probably other aetiological mechanisms. Further, there is less uncertainty about the prevalence of CP in the EPT population since this outcome is measured in most cohort studies. Our final sample included EPT children for whom we could define motor status, using the MABC-2, a commonly used and validated test of MD.

Our results confirmed a high prevalence of non-CP MD among five-year-old children born EPT, with over half at risk for MD (23.2%) or with significant MD (31.7%). We found unexplained variability in the prevalence of non-CP MD between countries, raising questions about the potential role of contextual factors on mitigation strategies. Furthermore, we identified multiple clinical risk factors for MD, namely low GA, SGA, male sex, severe brain lesions, BPD, receipt of postnatal corticosteroids, confirming that medical risks and serious illness in the perinatal period result in motor impairments later in childhood. In addition, several sociodemographic factors, including having younger, primiparous, less educated and non-European born mothers were associated with MD risks. Thus, family environment should be considered when preparing follow-up and early intervention programs. Less often examined in research, we were able to analyse children classified at risk for MD, also called mild motor impairment, and confirmed their high frequency among survivors of EPT birth.

This work is presented in its published form: *Pediatrics* (2022) (PMID: 35615946, DOI: [10.1542/peds.2021-054920](https://doi.org/10.1542/peds.2021-054920)) and reproduced according to American Academy of Pediatrics rights and permissions guidelines. Supplemental material is inserted at the end of the manuscript (*Supplemental material – Chapter 4*). These results were presented as a podium presentation at the 4th joint European Neonatal Societies Congress (Live Online Congress, 2021, September 14-18), and as poster presentation during the Doctoral school meetings (Saint-Malo, France, 2021, November 2-4) (Award of the best poster defence / Promotion 2020).

Movement Difficulties at Age Five Among Extremely Preterm Infants

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BACKGROUND AND OBJECTIVES: Children born extremely preterm (EPT), <28 weeks' gestational age, face higher risks of movement difficulties than their term-born peers. Studies report varying prevalence estimates and prognostic factors identifying children who could benefit from early intervention are inconsistent. This study investigated the prevalence of movement difficulties in children born EPT and associated risk factors.

METHODS: Data come from a population-based EPT birth cohort in 2011 and 2012 in 11 European countries. Children without cerebral palsy were assessed at 5 years of age ($N = 772$) with the Movement Assessment Battery for Children–Second Edition, which classifies movement difficulties as none (>15th percentile), at risk (6th–15th percentile) and significant (≤ 5 th percentile). Associations with sociodemographic, perinatal, and neonatal characteristics collected from obstetric and neonatal medical records and parental questionnaires were estimated using multinomial logistic regression.

RESULTS: We found 23.2% ($n = 179$) of children were at risk for movement difficulties and 31.7% ($n = 244$) had significant movement difficulties. Lower gestational age, severe brain lesions, and receipt of postnatal corticosteroids were associated with significant movement difficulties, whereas male sex and bronchopulmonary dysplasia were associated with being at risk and having significant movement difficulties. Children with younger, primiparous, less educated, and non-European-born mothers were more likely to have significant movement difficulties. Differences in prevalence between countries remained after population case-mix adjustments.

CONCLUSIONS: This study confirms a high prevalence of movement difficulties among EPT children without cerebral palsy, which are associated with perinatal and neonatal risk factors as well as sociodemographic characteristics and country.

abstract



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Mr Aubert and Drs Costa and Zeitlin conceptualized and designed the study, conducted the different analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Ådén and Johnson supervised the different analyses, and critically reviewed and revised the manuscript for important intellectual content; Drs Cuttini, Männamaa, Pierrat, Sarrechia, van Heijst, and Zemlin contributed to the study design, participated in data collection and curation, and critically reviewed and revised the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Movement difficulties are common among children born extremely preterm, but prevalence varies widely between studies. Male sex and gestational age seem to be the only 2 factors consistently associated with movement difficulties following extremely preterm birth.

WHAT THIS STUDY ADDS: In a large European cohort of children born extremely preterm, this study confirms a very high prevalence of movement difficulties and identifies multiple perinatal, neonatal, and sociodemographic risk factors for poor motor function at 5 years of age.

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With advances in obstetric and neonatal care, the survival of children born extremely preterm (EPT), <28 weeks' gestational age (GA), has increased in recent decades.¹⁻³ These children face higher risks of long-term developmental problems than children born at term, including cerebral palsy (CP) and a wide range of motor, sensory, cognitive, and behavioral impairments.⁴⁻⁶ In contrast with declining mortality and CP among EPT children, the prevalence of other neurodevelopmental impairments appears to have remained stable over time and has potentially increased.^{7,8} The lack of progress in developmental outcomes, accompanied by increasing numbers of survivors, makes research on the consequences of EPT birth a priority to enable early identification of developmental difficulties and timely referral for intervention at the individual and population levels.⁹

Movement difficulties are a common consequence of EPT birth.^{7,10-13} Movement difficulties can reduce the child's opportunities to develop in other areas and have been associated with impaired cognitive development, school performance, social integration, and functioning in adulthood.^{4,5,10,14-18} Despite this growing evidence base on the consequences of movement difficulties, our understanding of its prevalence and risk factors remains limited,^{12,19} particularly among children without CP.^{7,13,20} For instance, the prevalence of movement difficulties varies greatly between studies from 8%²¹ to >40%,^{13,18,20,22} likely because of population inclusion criteria, such as GA and birth weight thresholds and methodological differences. Recent reviews found inconsistent results in relation to early life risk factors with consistent associations with

motor impairment among children free of major disability only for male sex and preterm birth.^{6,12}

Reviews on motor function among children born very preterm have pointed to the lack of studies reporting the development of these children at school age, the lack of standardization of the measurement tools, the small and heterogeneous samples, as well as the failure to consider different clinical and sociodemographic characteristics that can strongly influence the results.^{4,12,23} Using data from a population-based European cohort of EPT children assessed using the Movement Assessment Battery for Children-Second Edition (Movement ABC-2),²⁴ this study aimed to estimate the prevalence of movement difficulties among 5-year-old children born EPT without CP in 19 regions from 11 European countries and to identify sociodemographic, perinatal, and neonatal risk factors associated with movement difficulties.

METHODS

Study Design and Participants

We used data from the Screening to Improve Health in Very Preterm Infants in Europe (SHIPS) study²⁵ that followed-up the Effective Perinatal Intensive Care in Europe population-based, prospective cohort of children born before 32 weeks' GA, between 2011 and 2012, in 19 regions in 11 European countries. Data were collected from obstetrical and neonatal records during the neonatal hospitalization using a standardized, pretested instrument by study investigators or medical personnel. When the child was 2 and 5 years of age, questionnaires on health, general development, and socioeconomic circumstances were sent to parents. Clinical assessments evaluating neurocognitive functioning and

motor skills (using the Movement ABC-2) were also conducted at 5 years of age for children born EPT.

Our study population was limited to children born EPT who were eligible for the Movement ABC-2 assessment. Out of 1671 EPT infants alive at discharge (Fig 1), 1654 were alive at 5 years, and 1021 were followed-up. As in most studies using the Movement ABC-2, we excluded children with a CP diagnosis ($n = 98$),²⁶⁻²⁸ as this is a well-defined neurodevelopmental disorder,²⁹ as well as children with a severe neurodevelopmental impairment defined as an intelligence quotient (IQ) ≤ 54 (< -3 standard deviation [SD]) or severe hearing or visual impairment ($n = 32$) because the Movement ABC-2 was not designed to assess movement abilities in these children.²⁴ Lastly, we excluded children with missing Movement ABC-2 data ($n = 119$): 88 children were assessed by parental questionnaire only, whereas in 31 the test was incomplete or missing and imputation was not possible. The final sample was comprised of 772 children.

Movement Difficulties

The Movement ABC-2,²⁴ is a validated test to evaluate movement difficulties by age category,^{10,30} even in high-risk populations of EPT children.²⁷ It assesses performance on 8 motor tasks in 3 motor components: manual dexterity, aiming and catching, and balance. Scores from all tests were summed and converted to an age adjusted percentile score based on United Kingdom norms that classify movement difficulties into 3 categories: none (> 15 th percentile), at risk (6th-15th percentile), and significant (≤ 5 th percentile), within each component and globally.²⁴ As national norms exist only in Belgium, France, Italy, the Netherlands, and the United Kingdom,^{24,31-33} we uniformly applied the United Kingdom norms that are the most commonly used in the literature.^{24,34} The Movement

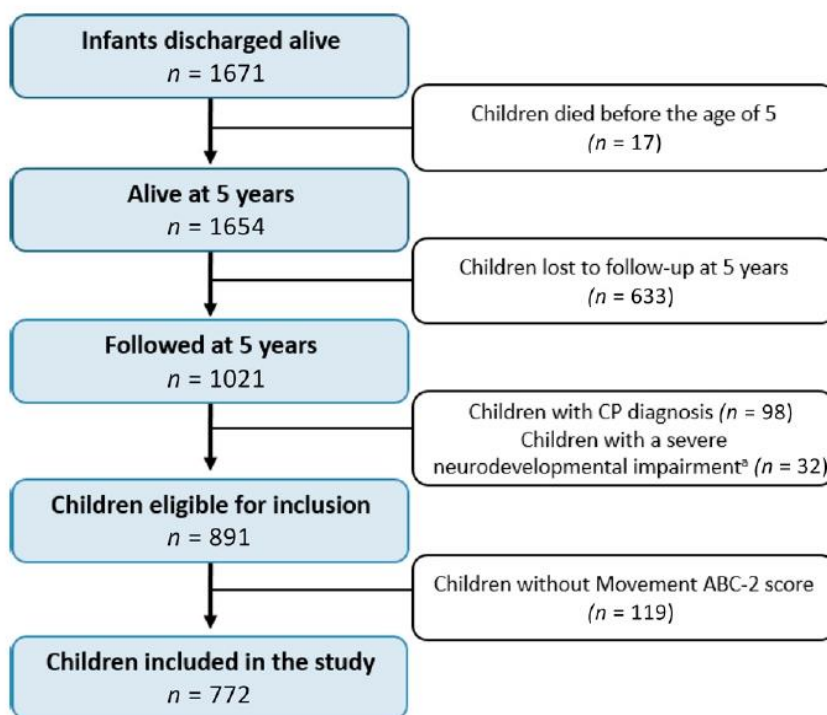


FIGURE 1
Flowchart of the sample selection from the SHIPS cohort (children born <28 gestational weeks). CP, cerebral palsy; Movement ABC-2, Movement Assessment Battery for Children—Second Edition^a Defined as an IQ ≤ 54 ($< -3SD$) or severe hearing or visual impairment.

ABC-2 was administered by trained psychologists or physiotherapists. Assessments were conducted by staff in local routine follow-up programs where available (Belgium, the Netherlands, and Sweden) or by the SHIPS research team (Denmark, Estonia, France, Germany, Italy, Poland, Portugal, and the United Kingdom). Although it was not possible to carry out interrater reliability across countries, common data collection guidelines and a core data collection form were developed to standardize procedures and to ensure consistent reporting of the assessment results. Training sessions were held locally, and an online discussion forum was set up to discuss possible problems emerging during the data collection.

Children who had missing Movement ABC-2 data were reviewed on a case-by-case basis by

neurodevelopmental specialists and an epidemiologist (R.C., U.A., S.J., and J.Z.). If a child was unable to complete a test-item or component because of severe motor impairment, the lowest score was assigned for that test-item and/or component ($n = 7$). If data were missing for a test-item or component score in the absence of other developmental problems, the average of the other test-items within the component was used for imputation ($n = 11$). For 11 Belgian children, percentile scores from the Movement ABC (First Edition) were used.³⁵ In all other cases, scores were left as missing.

Risk Factors

Variables selected for this analysis were those hypothesized to affect risks of movement difficulties based on biological plausibility and the scientific literature.

Sociodemographic factors included maternal age at childbirth, parity, maternal country of birth (from neonatal records), parental cohabiting status, maternal educational level,³⁶ and household unemployment status (from parental questionnaires). Perinatal and neonatal factors were GA, small for gestational age (SGA),³⁷ sex, multiple birth, premature rupture of membranes >12 hours, any antenatal corticosteroids, congenital anomaly,³⁸ severe brain lesions (intraventricular hemorrhage [IVH] grade III or IV or cystic periventricular leukomalacia [cPVL]), retinopathy of prematurity stage III or more, necrotizing enterocolitis (requiring surgery or peritoneal drainage), bronchopulmonary dysplasia ([BPD], defined as supplemental oxygen at 36 weeks' postmenstrual age), postnatal corticosteroids,³⁹ and breastfeeding at discharge.

Statistical Analyses

We first described the characteristics of children included in the sample and those excluded because of missing Movement ABC-2 scores. We then described the Movement ABC-2 classifications overall and by component. We produced 3 models to measure the association of sociodemographic, perinatal, and neonatal variables with the probability of being at risk or having significant movement difficulties using multinomial logistic regression taking into consideration clustering within multiple pairs: (1) with no adjustment except country modeled as a fixed effect (termed "unadjusted"), (2) adjusted on sociodemographic and perinatal factors, and (3) with additional adjustments on neonatal factors.

To take into account loss to follow-up, we used inverse probability weighting (IPW).^{40,41} As described previously for this cohort,⁴²⁻⁴⁴ we

compared the characteristics of responders and nonresponders at the 5-year follow-up (Supplemental Table 5). Variables potentially affecting loss to follow-up were used to estimate the probability of response using multivariate logistic regression and to define a weight inversely proportional to this probability (Supplemental Table 6). Multiple imputation by chained equations was used ($m = 20$) to impute missing data for covariates used to create the weights.^{45,46} We also imputed data for covariates in the final models ($m = 20$). Three had a percentage of missing >3.0%: household unemployment status (6.7%), parental cohabiting status (5.8%), and maternal education (4.0%). Data were assumed to be missing at random after taking into consideration observed covariates. We did not impute data for children with missing Movement ABC-2 scores as the missing at random assumptions likely did not hold. However, we compared the characteristics of children with and without Movement ABC-2 scores. Final models used IPW and multiple imputation.⁴⁷

We conducted sensitivity analyses by rerunning models (1) using the unweighted and complete case samples and (2) using national norms in the countries where these were available, as these may affect movement difficulties classification.³⁴

All analyses used the statistical software Stata version 15.0 (StataCorp, College Station, TX, USA).

RESULTS

Children in the study sample were assessed at 5.7 (0.4) years (mean SD) (Table 1). There were 28.6% born <26 weeks' GA, 49.8% were males, and 71.9% were singletons. Their mothers were aged 35 years or older for 26.1%, 58.5% were

primiparous, 37.0% had at least a bachelor's degree, and 18.6% were born outside of Europe. Compared with children in the sample, those without Movement ABC-2 scores were less likely to have young (<25 years) or old (≥ 35 years) mothers and were more likely to have lower GA and to not be breastfed at discharge from the neonatal unit. For children followed at 2 years of age, missing Movement ABC-2 scores were more common among those with impairment. Loss to follow-up was mainly related to social disadvantage and GA (Supplemental Table 5).

Movement Difficulties Among EPT Children

Children classified at risk and with significant movement difficulties comprised 23.2% and 31.7% of the sample, respectively (Table 2). The prevalence of significant movement difficulties was higher for the manual dexterity component (37.4%) than the aiming and catching and balance components (19.2% and 19.7%, respectively).

Risk Factors Associated With Movement Difficulties

The prevalence of movement difficulties by risk factor group as well as unadjusted relative risk ratios (RRR) and their 95% confidence intervals (95% CI) are presented in Table 3. Some factors had strong associations with both being at risk for movement difficulties and having significant movement difficulties (ie, household unemployment status, SGA, male sex, retinopathy of prematurity, and BPD), whereas some others were associated with significant movement difficulties only (ie, congenital anomalies, severe brain lesions, and postnatal corticosteroids). Prevalence of significant movement difficulties ranged from 12.4% (the Netherlands) to 72.3% (Poland),

whereas the at-risk group ranged from 11.3% (Sweden) to 39.0% (Belgium).

Adjustment on sociodemographic and perinatal factors (model I) slightly attenuated these associations (Table 4). Adjusting for neonatal factors (model II) further reduced the magnitude of associations of low GA, SGA, male sex, and congenital anomalies with significant movement difficulties. Severe brain lesions and postnatal corticosteroids were risk factors for significant movement difficulties, whereas BPD were risk factors for both at risk and significant movement difficulty groups. The other morbidities were no longer significant. These adjustments did not strongly impact the estimated associations with sociodemographic factors. The large differences between countries persisted in adjusted models.

Sensitivity analyses without IPW did not show differences in sample characteristics or prevalence of movement difficulties (Supplemental Tables 7 and 8), and final models using the unweighted and complete case samples yielded similar conclusions (Supplemental Table 9). Redoing models using Movement ABC-2 national norms (Supplemental Table 10) gave broadly similar results and did not affect study conclusions about the key risk factors or the wide variation between countries, although country rankings changed.

DISCUSSION

Among 772 European children born EPT without CP or severe neurodevelopmental impairment, 23.2% and 31.7% were classified as being at risk and having significant movement difficulties, respectively. Children with lower GA, severe brain lesions, and who received postnatal corticosteroids were more

TABLE 1 Characteristics of Children Included in the Study and Comparison With Children Who Had Missing Movement ABC-2 Scores (With IPW)

	Children Included in the Study ^a		Children Eligible for Inclusion but Without Movement ABC-2 ^a		<i>P</i> ^b
	<i>N</i> = 772	%	<i>N</i> = 119	%	
Sociodemographic characteristics					
Maternal age at childbirth, y					.001
<25	123	16.0	16	13.0	
25–34	446	57.9	87	73.5	
≥35	201	26.1	16	13.5	
Missing	2	0.3	0	0.1	
Parental cohabiting status					.89
Married, couple, or cohabiting	617	84.9	101	87.0	
Single or other	110	15.1	15	13.0	
Missing	45	5.8	3	2.5	
Maternal educational level					.88
≤Lower secondary	141	19.0	22	19.5	
Upper secondary or short tertiary	326	44.0	56	48.9	
≥Bachelor	274	37.0	36	31.6	
Missing	31	4.0	5	4.2	
Household unemployment status					
Employed or other situation ^c	623	86.5	93	81.9	
At least 1 parent unemployed	97	13.5	21	18.1	
Missing	52	6.7	5	4.2	
Parity					.75
First child	446	58.5	73	62.1	
Second child	180	23.6	27	22.8	
Third child or more	137	17.9	18	15.1	
Missing	9	1.2	1	0.8	
Maternal country of birth					.94
Native-born	570	74.1	87	72.9	
Other European country	57	7.4	7	6.0	
Non-European country	143	18.6	25	21.1	
Missing	3	0.4	0	0.0	
Perinatal and neonatal characteristics					
GA, wk					.03
≤24	93	12.0	19	16.1	
25	128	16.6	29	24.3	
26	231	29.9	30	24.8	
27	320	41.4	41	34.8	
Missing	0	0.0	0	0.1	
SGA					.24
<3rd percentile	114	14.8	15	12.9	
3rd–9th percentile	64	8.3	6	5.0	
≥10th percentile	594	77.0	98	82.1	
Missing	0	0.0	0	0.0	
Child sex					.19
Female	387	50.2	52	43.6	
Male	385	49.8	67	56.4	
Missing	0	0.0	0	0.0	
Multiple birth					.69
Singleton	555	71.9	84	70.8	
Multiple	217	28.1	35	29.2	
Missing	0	0.0	0	0.0	
Congenital anomaly					.96
No	719	93.2	109	91.6	
Yes	53	6.8	10	8.4	
Missing	0	0.0	0	0.0	
Severe neonatal morbidity ^d					.16
No	604	79.7	88	75.2	
Yes	153	20.3	29	24.8	
Missing	15	1.9	2	1.7	

TABLE 1 Continued

	Children Included in the Study ^a		Children Eligible for Inclusion but Without Movement ABC-2 ^a		<i>P</i> ^b
	<i>N</i> = 772	%	<i>N</i> = 119	%	
BPD					.30
No	500	66.5	82	70.0	
Yes	252	33.5	35	30.0	
Missing	20	2.6	2	1.7	
Breastfeeding at discharge					
No	343	45.1	70	60.8	
Yes	417	54.9	45	39.2	
Missing	12	1.6	4	3.4	
Characteristics of participants					
Age at assessment in years, mean (SD)	5.7	(0.4)	5.6	(0.4)	.90
Neurodevelopmental impairment ^c					.92
None	434	56.3	71	59.9	
Mild	255	33.1	36	30.0	
Moderate	82	10.7	12	10.0	
Missing	0	0.0	0	0.0	
Child development at 2 y of age ^f					
Global motor impairment ^g					.49
No	619	96.3	92	95.5	
Yes	24	3.7	4	4.5	
Missing	129	16.7	23	19.3	
Learning disability ^h					<.001
No	537	85.4	65	69.4	
Yes	92	14.6	29	30.6	
Missing	143	18.5	26	21.8	
Country (region)					
Belgium (Flanders)	50	6.5	9	7.7	
Denmark (eastern region)	46	6.0	10	8.1	
Estonia (entire country)	21	2.7	2	1.6	
France (Burgundy, Ile-de-France, northern region)	122	15.7	16	13.5	
Germany (Hesse, Saarland)	75	9.7	20	16.4	
Italy (Emilia-Romagna, Lazio, Marche)	98	12.6	24	19.8	
the Netherlands (central eastern)	50	6.5	2	1.9	
Poland (Wielkopolska)	24	3.1	9	7.8	
Portugal (Lisbon, northern region)	76	9.9	13	10.9	
United Kingdom (east midlands, northern, Yorkshire, and the Humber)	186	24.1	5	3.8	
Sweden (Greater Stockholm)	24	3.1	10	8.4	

^a Values are *N* rounded to a whole number; % (excluding missing values) rounded to 1 decimal, and mean (SD) for continuous variables, all with the use of inverse probability weighting (IPW) to correct loss to follow-up.

^b *P* values from Wald test of logistic regressions adjusted on country.

^c Other situations included student, parental leave, home parent, and other.

^d Included IVH grade III or IV, cPVL, retinopathy of prematurity stage III or more, and necrotizing enterocolitis.

^e Combined cognitive, hearing, and visual impairment.

^f Data from the parental questionnaire filled at 2 y corrected age: 647 over 772 (83.8%) and 96 over 119 (80.7%) children have been followed at this stage.

^g Global motor impairment at 2 y of age estimated from 3 parental-reported questions on abilities on walking, sitting, and head holding.

^h Learning disability at 2 y of age estimated from the Parent Report of Children's Abilities-Revised (or the Ages and Stages Questionnaires for France only).

likely to have significant movement difficulties, whereas SGA (ie, <3rd percentile), male sex, and BPD were associated with both being at risk and having significant movement difficulties. Sociodemographic factors, including having younger, primiparous, less educated, and non-European born mothers, were

associated with movement difficulties risks. Wide variations in prevalence existed by country and these persisted after adjustment for individual characteristics.

Prevalence of Movement Difficulties

Although children born EPT are more likely to have movement

difficulties compared with their term-born peers,^{6,10,20,48} prevalence estimates reported in the literature vary by a factor of 5.^{13,18,20-22} Some of this variability results from the use of different motor function measures, including parental report,⁴⁹ Movement ABC or other tests,^{6,10,12} ages of assessment, and

TABLE 2 Rates of Movement Difficulties, in Total and by Component (Based on Movement ABC-2)

	Movement Difficulties ^a					
	None (>15th Percentile)		At Risk (6th–15th Percentile) ^b		Significant (≤5th Percentile)	
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%
Total ^c	349	45.2	179	23.2	244	31.7
Manual dexterity ^d	313	41.2	162	21.3	284	37.4
Aiming and catching ^d	542	71.5	71	9.4	145	19.2
Balance ^d	478	63.0	131	17.3	149	19.7

^a Values are *N* rounded to a whole number and % (excluding missing values) rounded to 1 decimal; both with the use of inverse probability weighting (IPW) to correct loss to follow-up.

^b As explained in the Movement ABC-2 manual,²⁴ the 16th percentile is used instead of the 15th percentile to delineate the “at risk of movement difficulties” category.

^c Total: Movement ABC-2 total score composed of the 3 components (manual dexterity, aiming and catching, and balance).

^d For the 3 component scores, the total of the *n* is not necessarily equal to 772 because mainly total scores were imputed when a test-item or a component was missing.

population inclusion criteria.²⁰ When comparisons are restricted to studies with samples and methods similar to ours, prevalence is higher with lower variability. For instance, 37.1% of children had Movement ABC-2 scores ≤5th percentile in a Swedish sample born <27 weeks’ GA, after exclusion of children with CP or severe neurodevelopmental impairment.¹³ In an Australian sample of 165 children born <30 weeks’ GA or <1250 g birth weight without CP or IQ <80 points, 47.9% had a Movement ABC (First Edition) score ≤16th percentile.¹⁸ Nonetheless, contextual variations in prevalence persist even between these more standardized samples, as we observed within our European cohort by the differences between countries. Variation is also seen in proportions classified as being at risk or with significant movement difficulties, with some studies finding more children in the most severe category,⁵⁰ as we did. This heavily skewed distribution of scores reflects the high levels of impairment in this population. Finally, when movement difficulties were classified by component, we noted a lower prevalence of impairment for aiming and catching and balance (19% to 20% with significant movement difficulties), compared with manual dexterity

(37%). Two previous reviews also noted differences by domain, with lower performance in manual dexterity in some, but not all studies.^{10,50}

Risk Factors

Some perinatal and neonatal characteristics associated with movement difficulties were reported previously,^{6,12,50} including lower GA, SGA, male sex, severe brain lesions, BPD, and postnatal corticosteroids.^{27,51} In a recent review, Van Hoorn et al,⁶ reported on several studies showing associations between neonatal brain lesions and motor development. In addition, use of postnatal corticosteroids was associated with motor impairment in 2 out of 3 studies. The risk of developmental coordination disorder (measured by Movement ABC in 22 of 36 studies), was generally inversely related to the GA group, an association found in our sample. Contrary to some reports, premature rupture of membranes, necrotizing enterocolitis, and retinopathy of prematurity were not associated with movement difficulties.^{51–53} However, these associations have been inconsistent in the literature^{6,12} and may be influenced by population differences (eg, inclusion of children with other

major disabilities),⁵² or methods for measuring comorbidities.⁵¹ Finally, we found that children who did not receive antenatal corticosteroids were less likely to be at risk for movement difficulties, an association not previously reported⁶; however, as few children were in this group, this may be a spurious finding. Being able to identify children at risk using perinatal and neonatal risk profiles has the potential to improve long-term motor outcomes as studies find beneficial effects of early intervention.^{54,55} Further, the identification of risk factors can generate etiological hypotheses; our finding that risk profiles differed for children classified as at risk versus with significant movement difficulties, requiring confirmation in future work, may suggest varying causal pathways.

Several sociodemographic characteristics increased risks of movement difficulties: low maternal age, lower educational level, parental unemployment, primiparity, and non-European maternal country of birth. Previous studies have reported associations with some sociodemographic characteristics, but often only 1 or 2 characteristics and among younger children below 5 years of age.^{12,56–59} Null or contradictory findings may result from sociodemographic factors not being consistently or fully explored.^{6,12,50} Understanding how social factors interact with medical and biological risk is an important area for study since it makes it possible to target at-risk groups and understand risk and resilience mechanisms.

After adjustment on sociodemographic and clinical factors, differences in movement difficulties persisted by country of birth. We also found that prevalence estimates at the country-level were sensitive to the choice of norm, as previously shown.³⁴ Taken together,

TABLE 3 Sociodemographic, Perinatal, and Neonatal Characteristics Over Movement Difficulties Classification (Based on Movement ABC-2)

	N =	Movement Difficulties ^a					
		None		At risk		Significant	
		%	%	Unadjusted RRR (95% CI)	%	Unadjusted RRR (95% CI)	
	772	45.2	23.2		31.7		
Sociodemographic characteristics							
Maternal age at childbirth, y							
<25	123	29.2	24.8	1.80	(0.91–3.57)	45.9	2.71 (1.39–5.29)
25–34	446	46.2	24.6		REF	29.2	REF
≥35	201	53.4	17.6	0.65	(0.41–1.01)	29.0	0.91 (0.59–1.40)
Parental cohabiting status							
Married, couple, or cohabiting	617	46.6	22.2		REF	31.2	REF
Single or other	110	45.7	28.0	1.38	(0.75–2.53)	26.3	1.03 (0.54–1.96)
Maternal educational level							
≤Lower secondary	141	38.9	22.0	1.40	(0.76–2.56)	39.1	2.69 (1.47–4.90)
Upper secondary or short tertiary	326	45.4	22.2	0.99	(0.63–1.57)	32.4	1.21 (0.76–1.93)
≥Bachelor	274	49.2	24.5		REF	26.3	REF
Household unemployment status							
Employed or other situation ^b	623	49.3	21.7		REF	29.0	REF
At least 1 parent unemployed	97	29.9	31.4	2.61	(1.35–5.07)	38.7	2.20 (1.04–4.68)
Parity							
Primiparous	446	41.9	25.2	1.47	(0.97–2.24)	32.9	1.48 (0.97–2.25)
Multiparous	317	49.4	20.1		REF	30.5	REF
Maternal country of birth							
Native-born	570	44.3	25.1		REF	30.5	REF
Other European country	57	40.2	24.7	1.16	(0.53–2.52)	35.1	1.34 (0.64–2.83)
Non-European country	143	50.2	14.2	0.58	(0.31–1.11)	35.6	1.51 (0.83–2.77)
Perinatal characteristics							
GA, wk							
≤24	93	26.8	22.1	1.88	(0.95–3.70)	51.1	4.09 (2.16–7.75)
25	128	38.5	19.4	1.18	(0.66–2.10)	42.1	2.65 (1.52–4.61)
26	231	47.7	24.7	1.17	(0.73–1.86)	27.6	1.31 (0.79–2.18)
27	320	51.3	23.9		REF	24.8	REF
SGA							
<3rd percentile	114	34.3	28.8	2.04	(1.21–3.45)	36.9	2.00 (1.19–3.38)
3rd–9th percentile	64	45.5	18.7	0.86	(0.43–1.74)	35.8	1.17 (0.61–2.28)
≥10th percentile	594	47.2	22.6		REF	30.2	REF
Child sex							
Female	387	53.5	21.3		REF	25.2	REF
Male	385	36.8	25.0	1.77	(1.19–2.63)	38.2	2.46 (1.61–3.74)
Multiple birth							
Singleton	555	41.6	24.1		REF	34.3	REF
Multiple	217	54.3	20.8	0.63	(0.41–0.97)	24.9	0.59 (0.37–0.95)
Premature rupture of membranes							
No	562	45.0	22.5		REF	32.5	REF
Yes	201	45.3	24.8	1.19	(0.76–1.85)	30.0	1.00 (0.63–1.61)
Antenatal corticosteroids							
No	81	54.7	13.5	0.42	(0.19–0.90)	31.9	0.83 (0.39–1.77)
Yes	686	44.2	24.1		REF	31.7	REF
Congenital anomaly							
No	719	45.6	23.8		REF	30.7	REF
Yes	53	39.3	15.2	0.92	(0.39–2.19)	45.5	2.37 (1.02–5.53)
Neonatal characteristics							
Severe brain lesions (IVH or cPVL) ^c							
No	697	46.9	23.5		REF	29.5	REF
Yes	70	28.7	19.1	1.34	(0.66–2.72)	52.2	3.11 (1.69–5.73)
Retinopathy of prematurity							
No	678	48.1	23.1		REF	28.8	REF
Yes	83	22.0	23.1	2.18	(1.08–4.39)	54.9	3.59 (1.88–6.86)
Necrotizing enterocolitis							
No	740	45.8	22.8		REF	31.4	REF
Yes	32	30.5	32.0	1.75	(0.57–5.33)	37.5	1.37 (0.41–4.63)

TABLE 3 Continued

	Movement Difficulties ^a						
	N =	None		At risk		Significant	
		772	%	%	Unadjusted RRR	%	Unadjusted RRR
		45.2	23.2	(95% CI)	31.7	(95% CI)	
BPD							
No	500	53.9	22.0	REF	24.1	REF	
Yes	252	27.4	25.7	2.25 (1.41–3.59)	46.9	3.65 (2.32–5.73)	
Postnatal corticosteroids							
No	541	50.2	23.6	REF	26.1	REF	
Yes	220	33.2	21.2	1.56 (0.98–2.46)	45.7	3.55 (2.23–5.65)	
Breastfeeding at discharge							
No	343	39.4	23.5	1.38 (0.91–2.11)	37.1	1.69 (1.11–2.59)	
Yes	417	50.0	23.1	REF	26.9	REF	
Country (region)							
Belgium (Flanders)	50	36.5	39.0	REF	24.5	REF	
Denmark (eastern region)	46	52.4	28.1	0.49 (0.19–1.31)	19.6	0.39 (0.14–1.12)	
Estonia (entire country)	21	57.6	12.1	0.19 (0.05–0.69)	30.3	0.56 (0.21–1.46)	
France (Burgundy, Ile-de-France, northern region)	122	69.9	17.2	0.23 (0.10–0.50)	12.8	0.32 (0.15–0.67)	
Germany (Hesse, Saarland)	75	51.1	16.6	0.29 (0.11–0.78)	32.3	0.89 (0.38–2.08)	
Italy (Emilia–Romagna, Lazio, Marche)	98	40.0	23.8	0.57 (0.26–1.25)	36.2	1.10 (0.53–2.28)	
the Netherlands (central eastern)	50	53.9	33.8	0.58 (0.25–1.33)	12.4	0.28 (0.11–0.68)	
Poland (Wielkopolska)	24	15.6	12.1	0.60 (0.14–2.65)	72.3	4.22 (1.36–13.15)	
Portugal (Lisbon, northern region)	76	41.2	29.3	0.64 (0.28–1.45)	29.6	0.83 (0.37–1.85)	
United Kingdom (east midlands, northern, Yorkshire, and the Humber)	186	30.2	22.7	0.70 (0.30–1.60)	47.1	1.92 (0.89–4.14)	
Sweden (Greater Stockholm)	24	56.8	11.3	0.18 (0.04–0.75)	31.9	0.56 (0.20–1.58)	

REF, reference category.

^a Values are N rounded to a whole number, % (excluding missing values) rounded to 1 decimal, and RRR and their 95% CI using multinomial logistic regression taking into consideration clustering within multiple pairs, with country modeled as a fixed effect; all with the use of IPW to correct loss to follow-up.

^b Other situations included student, parental leave, home parent, and other.

^c Severe brain lesions, defined as having an IVH grade III or IV, and/or a cPVL.

these results raise the possibility that cultural, or policy factors could affect motor outcomes for children born EPT. For instance, preschool, school, or public health programs which differ between European countries^{60–62} may influence general motor development and subsequently affect performance on Movement ABC tests, even for children born EPT.^{63–65} Further research to confirm and investigate cross-country differences in movement difficulties could inform prevention efforts.

Strengths and Limitations

The main strengths of this study are its large, population-based sample of >750 EPT children, standardized collection of sociodemographic, perinatal, and neonatal data and the measurement of movement difficulties using a validated and

widely used clinical assessment.^{10,12} Few studies have been conducted on prognostic factors for motor impairment in EPT children without CP and most studies of Movement ABC-2 have much smaller samples.¹² To harmonize results between countries, we applied the Movement ABC-2 United Kingdom norms²⁴ and were able to conduct sensitivity analyses to confirm that risk factor results were robust to use of national norms. An additional strength is that we analyzed children at risk for movement difficulties as well as those with significant movement difficulties. Minor difficulties are less often examined, but they may substantially impact quality of life and have been identified as an important priority for future investigation.⁹

Limits include possible attrition bias because of loss to follow-up (61.7%

follow-up at 5 years) or bias because of children with a missing Movement ABC-2 score. Because we have full data on the cohort at inclusion, these biases could be described and we were able to use IPW to adjust for loss to follow-up, principally related to social factors, as found in other cohorts.^{42–44} In contrast, we did not use statistical methods to adjust for bias because of missing Movement ABC-2 scores. These children were a higher risk subgroup and their Movement ABC-2 assessments were likely not missing at random. This may lead to underestimation of movement difficulties in this population. Further, we found large differences in movement difficulties prevalence between countries but could not explore them in more detail because of

TABLE 4 Association Between Movement Difficulties and Sociodemographic and Perinatal (Model I), and Neonatal (Model II) Characteristics Among 5-Year-Old Children Born Extremely Preterm (*N* = 772)

	At Risk for Movement Difficulties ^a				Significant Movement Difficulties ^a			
	Model I		Model II		Model I		Model II	
	RRR (95% CI)		RRR (95% CI)		RRR (95% CI)		RRR (95% CI)	
Sociodemographic characteristics								
Maternal age at childbirth, y								
<25	1.52	(0.72–3.24)	1.74	(0.79–3.84)	2.22	(1.09–4.50)	2.47	(1.15–5.30)
25–34		REF		REF		REF		REF
≥35	0.70	(0.42–1.17)	0.71	(0.43–1.17)	1.11	(0.68–1.81)	1.10	(0.67–1.80)
Parental cohabiting status								
Married, couple, or cohabiting		REF		REF		REF		REF
Single or other	1.41	(0.74–2.69)	1.42	(0.74–2.75)	0.89	(0.41–1.95)	0.91	(0.42–1.95)
Maternal educational level								
≤Lower secondary	1.22	(0.59–2.51)	1.21	(0.58–2.54)	2.14	(0.99–4.65)	2.26	(1.01–5.04)
Upper secondary or short tertiary	0.89	(0.54–1.47)	0.87	(0.53–1.45)	1.04	(0.60–1.78)	1.02	(0.59–1.80)
≥Bachelor		REF		REF		REF		REF
Household unemployment status								
Employed or other situation ^b		REF		REF		REF		REF
At least 1 parent unemployed	3.14	(1.56–6.33)	3.16	(1.58–6.31)	2.00	(0.88–4.55)	1.96	(0.87–4.43)
Parity								
Primiparous	1.43	(0.90–2.27)	1.50	(0.94–2.42)	1.77	(1.10–2.85)	1.76	(1.07–2.91)
Multiparous		REF		REF		REF		REF
Maternal country of birth								
Native-born		REF		REF		REF		REF
Other European country	0.97	(0.43–2.18)	1.04	(0.44–2.43)	1.34	(0.59–3.05)	1.50	(0.62–3.61)
Non-European country	0.53	(0.27–1.04)	0.54	(0.27–1.08)	1.74	(0.95–3.18)	1.90	(1.04–3.46)
Perinatal characteristics								
GA, wk								
≤24	1.84	(0.85–3.99)	1.45	(0.62–3.44)	4.86	(2.38–9.92)	2.30	(1.03–5.13)
25	1.26	(0.69–2.28)	1.10	(0.59–2.07)	3.51	(1.94–6.32)	2.42	(1.31–4.48)
26	1.25	(0.76–2.05)	1.17	(0.71–1.93)	1.60	(0.92–2.79)	1.34	(0.76–2.36)
27		REF		REF		REF		REF
SGA								
<3 rd percentile	2.19	(1.25–3.84)	1.82	(1.00–3.30)	2.34	(1.27–4.29)	1.59	(0.83–3.04)
3 rd –9 th percentile	1.09	(0.51–2.30)	1.02	(0.47–2.18)	1.78	(0.83–3.79)	1.58	(0.73–3.40)
≥10 th percentile		REF		REF		REF		REF
Child sex								
Female		REF		REF		REF		REF
Male	1.88	(1.24–2.86)	1.81	(1.18–2.76)	2.62	(1.68–4.08)	2.23	(1.42–3.51)
Multiple birth								
Singleton		REF		REF		REF		REF
Multiple	0.67	(0.44–1.03)	0.65	(0.42–1.01)	0.79	(0.48–1.31)	0.78	(0.46–1.33)
Premature rupture of membranes								
No		REF		REF		REF		REF
Yes	1.12	(0.69–1.84)	1.14	(0.69–1.88)	1.02	(0.61–1.69)	1.04	(0.62–1.72)
Antenatal corticosteroids								
No	0.36	(0.16–0.84)	0.35	(0.15–0.81)	0.86	(0.37–2.02)	0.80	(0.33–1.96)
Yes		REF		REF		REF		REF
Congenital anomaly								
No		REF		REF		REF		REF
Yes	0.69	(0.27–1.75)	0.69	(0.27–1.76)	2.28	(0.92–5.64)	2.33	(0.95–5.72)
Neonatal characteristics								
Severe brain lesions (IVH or cPVL) ^c								
No				REF				REF
Yes			1.31	(0.63–2.73)			2.17	(1.14–4.12)
Retinopathy of prematurity								
No				REF				REF
Yes			1.21	(0.53–2.75)			1.34	(0.66–2.76)
Necrotizing enterocolitis								
No				REF				REF
Yes			1.54	(0.57–4.19)			1.10	(0.41–2.96)

TABLE 4 Continued

	At Risk for Movement Difficulties ^a				Significant Movement Difficulties ^a			
	Model I		Model II		Model I		Model II	
	RRR (95% CI)		RRR (95% CI)		RRR (95% CI)		RRR (95% CI)	
BPD								
No			REF				REF	
Yes			1.94 (1.13–3.33)				2.54 (1.47–4.40)	
Postnatal corticosteroids								
No			REF				REF	
Yes			1.05 (0.61–1.82)				1.94 (1.09–3.44)	
Breastfeeding at discharge								
No			1.01 (0.62–1.64)				0.98 (0.59–1.62)	
Yes			REF				REF	
Country (region)								
Belgium (Flanders)		REF	REF		REF		REF	
Denmark (eastern region)	0.40 (0.14–1.13)		0.42 (0.15–1.19)		0.63 (0.18–2.18)		0.66 (0.20–2.21)	
Estonia (entire country)	0.15 (0.04–0.55)		0.16 (0.04–0.59)		0.85 (0.28–2.60)		0.85 (0.26–2.82)	
France (Burgundy, Ile-de-France, Northern Region)	0.18 (0.08–0.43)		0.19 (0.08–0.47)		0.21 (0.07–0.56)		0.20 (0.07–0.54)	
Germany (Hesse, Saarland)	0.21 (0.07–0.61)		0.24 (0.08–0.72)		0.57 (0.19–1.72)		0.64 (0.21–1.97)	
Italy (Emilia-Romagna, Lazio, Marche)	0.53 (0.23–1.25)		0.56 (0.23–1.35)		1.85 (0.72–4.78)		1.80 (0.70–4.64)	
the Netherlands (central eastern)	0.55 (0.22–1.33)		0.52 (0.21–1.29)		0.31 (0.10–0.98)		0.26 (0.08–0.88)	
Poland (Wielkopolska)	0.70 (0.13–3.65)		0.81 (0.15–4.35)		8.75 (1.98–38.59)		9.61 (2.09–44.17)	
Portugal (Lisbon, northern region)	0.52 (0.22–1.26)		0.55 (0.22–1.37)		1.10 (0.41–2.98)		1.15 (0.42–3.17)	
United Kingdom (east midlands, northern, Yorkshire, and the Humber)	0.63 (0.27–1.48)		0.53 (0.22–1.32)		3.03 (1.16–7.91)		2.46 (0.87–6.92)	
Sweden (Greater Stockholm)	0.15 (0.03–0.68)		0.14 (0.03–0.67)		0.56 (0.15–2.06)		0.61 (0.15–2.44)	

REF, reference category.

^a Values are RRR and their 95% CI from multinomial logistic regression models: adjusted on sociodemographic and perinatal factors (Model I) and adjusted additionally on neonatal factors (Model II); both taking into consideration clustering within multiple pairs, with country modeled as a fixed effect, and with the use of IPW and multiple imputed dataset.

^b Other situations included student, parental leave, home parent, and other.

^c Severe brain lesions, defined as having an IVH grade III or IV, and/or a cPVL.

limited sample sizes per country. We did not have a control population of children born at term, however studies with controls report good calibration of Movement ABC-2 norms in their control samples.⁵⁰ Although test and examiner reliabilities across sites were not assessed, recommendations by the European Academy of Childhood Disability on developmental coordination disorder concluded that the Movement ABC-2 has good to excellent interrater reliability and test-retest reliability.¹⁷ A final limitation is the study's observational design and the measurement of some sociodemographic characteristics at the same time as our study outcome. However, our objective

was to identify risk-factor associations, not determine causality.⁶⁶

CONCLUSIONS

In this large population-based sample of 5-year-old children born EPT in Europe without CP, we found that over half were at risk for movement difficulties or had significant movement difficulties. We identified multiple clinical risk factors that could be used to prioritize at-risk children for follow-up and early intervention services. We also showed associations with social factors illustrating the importance of integrating social circumstances into public health programs for children born EPT. Finally, our study found unexplained variability in the prevalence of at

risk for or significant movement difficulties by country that raise questions about the role of the broader social or health context in mitigating risks in this population.

Ethical Approval

All study regions obtained ethical approval according to national legislations. The study was also approved by the French Advisory Committee on Use of Health Data in Medical Research and the French National Commission for Data Protection and Liberties. Parents gave their written informed consent to participating in the study before any data collection.

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ABBREVIATIONS

BPD: bronchopulmonary dysplasia
CI: confidence interval
CP: cerebral palsy
cPVL: cystic periventricular leukomalacia
EPT: extremely preterm
GA: gestational age
IPW: inverse probability weighting
IQ: intelligence quotient
IVH: intraventricular hemorrhage
Movement ABC-2: Movement Assessment Battery for Children—Second Edition
RRR: relative risk ratio
SD: standard deviation
SGA: small for gestational age
SHIPS: Screening to Improve Health in Very Preterm Infants in Europe

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REFERENCES

1. Tucker J, McGuire W. Epidemiology of preterm birth. *BMJ*. 2004;329(7467):675–678
2. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371(9606):75–84
3. Stoll BJ, Hansen NI, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA*. 2015;314(10):1039–1051
4. Moreira RS, Magalhães LC, Alves CRL. Effect of preterm birth on motor development, behavior, and school performance of school-age children: a systematic review. *J Pediatr (Rio J)*. 2014;90(2):119–134
5. Allotey J, Zamora J, Cheong-See F, et al. Cognitive, motor, behavioural and academic performances of children born preterm: a meta-analysis and systematic review involving 64 061 children. *BJOG*. 2018;125(1):16–25
6. van Hoorn JF, Schoemaker MM, Stuive I, et al. Risk factors in early life for developmental coordination disorder: a scoping review. *Dev Med Child Neurol*. 2021; 63(5):511–519

7. Spittle AJ, Cameron K, Doyle LW, Cheong JL; Victorian Infant Collaborative Study Group. Motor impairment trends in extremely preterm children: 1991-2005. *Pediatrics*. 2018;141(4):e20173410
8. Cheong JLY, Olsen JE, Lee KJ, et al; Victorian Infant Collaborative Study Group. Temporal trends in neurodevelopmental outcomes to 2 Years after extremely preterm birth. *JAMA Pediatr*. 2021; 175(10):1035–1042
9. Zeitlin J, Sentenac M, Morgan AS, et al; RECAP Preterm child cohort research group. Priorities for collaborative research using very preterm birth cohorts. *Arch Dis Child Fetal Neonatal Ed*. 2020;105(5):538–544
10. de Kieviet JF, Piek JP, Aarnoudse-Moens CS, Oosterlaan J. Motor development in very preterm and very low-birth-weight children from birth to adolescence: a meta-analysis. *JAMA*. 2009;302(20): 2235–2242
11. Baron IS, Rey-Casserly C. Extremely preterm birth outcome: a review of four decades of cognitive research. *Neuropsychol Rev*. 2010;20(4):430–452
12. Linsell L, Malouf R, Morris J, Kurinczuk JJ, Marlow N. Prognostic factors for cerebral palsy and motor impairment in children born very preterm or very low birthweight: a systematic review. *Dev Med Child Neurol*. 2016;58(6):554–569
13. 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
14. 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
15. Husby IM, Stray KMT, Olsen A, et al. Long-term follow-up of mental health, health-related quality of life and associations with motor skills in young adults born preterm with very low birth weight. *Health Qual Life Outcomes*. 2016;14:56
16. Oudgenoeg-Paz O, Mulder H, Jongmans MJ, van der Ham IJM, Van der Stigchel S. The link between motor and cognitive development in children born preterm and/or with low birth weight: a review of current evidence. *Neurosci Biobehav Rev*. 2017;80:382–393
17. 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;61(3):242–285
18. Spittle AJ, Dewey D, Nguyen TNN, et al. Rates of developmental coordination disorder in children born very preterm. *J Pediatr*. 2021;231:61–67.e2
19. Golding J, Emmett P, Iles-Caven Y, Steer C, Lingam R. A review of environmental contributions to childhood motor skills. *J Child Neurol*. 2014;29(11):1531–1547
20. Williams J, Lee KJ, Anderson PJ. Prevalence of motor-skill impairment in preterm children who do not develop cerebral palsy: a systematic review. *Dev Med Child Neurol*. 2010;52(3): 232–237
21. Setänen S, Lehtonen L, Parkkola R, Matomäki J, Haataja L. The motor profile of preterm infants at 11 y of age. *Pediatr Res*. 2016;80(3):389–394
22. Bos AF, Van Braeckel KNJA, Hitzert MM, Tanis JC, Roze E. Development of fine motor skills in preterm infants. *Dev Med Child Neurol*. 2013;55(Suppl 4):1–4
23. Linsell L, Malouf R, Morris J, Kurinczuk JJ, Marlow N. Risk factor models for neurodevelopmental outcomes in children born very preterm or with very low birth weight: a systematic review of methodology and reporting. *Am J Epidemiol*. 2017;185(7):601–612
24. Henderson SE, Sugden DA, Barnett AL. *Movement Assessment Battery for Children-2* (2nd Ed.). Psychological corporation; 2007
25. Zeitlin J, Maier RF, Cuttini M, et al; EPICE and SHIPS Research Group. Cohort profile: effective perinatal intensive care in Europe (EPICE) very preterm birth cohort. *Int J Epidemiol*. 2020;49(2):372–386
26. Janssen AJWM, Nijhuis-van der Sanden MW, Akkermans RP, Tissingh J, Oostendorp RA, Kollée LA. A model to predict motor performance in preterm infants at 5 years. *Early Hum Dev*. 2009;85(9):599–604
27. Dewey D, Creighton DE, Heath JA, et al. Assessment of developmental coordination disorder in children born with extremely low birth weights. *Dev Neuropsychol*. 2011;36(1):42–56
28. Janssen AJWM, Oostendorp RAB, Akkermans RP, Steiner K, Kollée LAA, Nijhuis-van der Sanden MWG. High variability of individual longitudinal motor performance over five years in very preterm infants. *Res Dev Disabil*. 2016;59:306–317
29. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl*. 2007;109:8–14
30. Blank R, Smits-Engelsman B, Polatajko H, Wilson P; European Academy for Childhood Disability. European Academy for Childhood Disability (EACD): recommendations on the definition, diagnosis and intervention of developmental coordination disorder (long version). *Dev Med Child Neurol*. 2012;54(1):54–93
31. Smits-Engelsman B. *Movement Assessment Battery for Children-2, Dutch Adaptation*, 2nd ed. Pearson Assessment; 2010
32. Marquet-Doléac J, Soppelsa R, Albaret JM. *Movement Assessment Battery for Children-2, French Adaptation*, 2nd ed. Pearson France-ECPA; 2016
33. Biancotto M, Borean M, Bravar L, Pelamatti GM, Zoia S. *Movement Assessment Battery for Children-2, Italian Adaptation*, 2nd ed. Giunti O.S.; 2013
34. Costa R, Johnson S, Cuttini M, et al. The impact of choice of norms on classification of motor impairment for children born very preterm. *Early Hum Dev*. 2020;146:105056.
35. Henderson SE, Sugden DA. *Movement assessment battery for children*. London: The Psychological Corporation; 2021
36. UNESCO Institute for Statistics. International standard classification of education: ISCED 2011. Available at: <http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-isced-2011-en.pdf>. Accessed September 20, 2021
37. Zeitlin J, Bonamy AKE, Piedvache A, et al. Variation in term birthweight across European countries affects the prevalence of small for gestational age among very preterm infants. *Acta Paediatr*. 2017;106(9):1447–1455

38. Draper ES, Manktelow BN, Cuttini M, et al; EPICE Cohort. Variability in very preterm stillbirth and in-hospital mortality across Europe. *Pediatrics*. 2017;139(4):e20161990
39. Nuytten A, Behal H, Duhamel A, et al; EPICE (Effective Perinatal Intensive Care in Europe) Research Group. Evidence-based neonatal unit practices and determinants of postnatal corticosteroid-use in preterm births below 30 weeks GA in Europe. a population-based cohort study. *PLoS One*. 2017;12(1):e0170234
40. Hernán MA, Robins JM. Estimating causal effects from epidemiological data. *J Epidemiol Community Health*. 2006;60(7):578–586
41. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res*. 2013;22(3):278–295
42. Bonnet C, Blondel B, Piedvache A, et al; EPICE Research Group. Low breastfeeding continuation to 6 months for very preterm infants: a European multiregional cohort study. *Matern Child Nutr*. 2019;15(1):e12657
43. Seppänen AV, Sauvegrain P, Draper ES, et al; SHIPS Research Group. Parents' ratings of post-discharge healthcare for their children born very preterm and their suggestions for improvement: a European cohort study. *Pediatr Res*. 2021;89(4):1004–1012
44. Piedvache A, van Buuren S, Barros H, Ribeiro AI, Draper E, Zeitlin J; EPICE Research group. Strategies for assessing the impact of loss to follow-up on estimates of neurodevelopmental impairment in a very preterm cohort at 2 years of age. *BMC Med Res Methodol*. 2021;21(1):118
45. Royston P, White IR. Multiple imputation by chained equations (MICE): implementation in stata. *J Stat Softw*. 2011;45(1):1–20
46. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30(4):377–399
47. Seaman SR, White IR, Copas AJ, Li L. Combining multiple imputation and inverse-probability weighting. *Biometrics*. 2012;68(1):129–137
48. Edwards J, Berube M, Erlandson K, et al. Developmental coordination disorder in school-aged children born very preterm and/or at very low birth weight: a systematic review. *J Dev Behav Pediatr*. 2011;32(9):678–687
49. Caravale B, Herich L, Zoia S, et al. Risk of developmental coordination disorder in Italian very preterm children at school age compared to general population controls. *Eur J Paediatr Neurol*. 2019;23(2):296–303
50. Evensen KAI, Ustad T, Tikanmäki M, Haaramo P, Kajantie E. Long-term motor outcomes of very preterm and/or very low birth weight individuals without cerebral palsy: a review of the current evidence. *Semin Fetal Neonatal Med*. 2020;25(3):101116
51. Lean RE, Paul RA, Smyser TA, Smyser CD, Rogers CE. Social adversity and cognitive, language, and motor development of very preterm children from 2 to 5 years of age. *J Pediatr*. 2018;203:177–184.e1
52. Taylor HG, Klein N, Drotar D, Schluchter M, Hack M. Consequences and risks of <1000-g birth weight for neuropsychological skills, achievement, and adaptive functioning. *J Dev Behav Pediatr*. 2006;27(6):459–469
53. Goyen TA, Lui K. Developmental coordination disorder in “apparently normal” schoolchildren born extremely preterm. *Arch Dis Child*. 2009;94(4):298–302
54. Smits-Engelsman BCM, Blank R, van der Kaay AC, et al. Efficacy of interventions to improve motor performance in children with developmental coordination disorder: a combined systematic review and meta-analysis. *Dev Med Child Neurol*. 2013;55(3):229–237
55. Spittle A, Orton J, Anderson PJ, Boyd R, Doyle LW. Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. *Cochrane Database Syst Rev*. 2015;(11):CD005495
56. Vohr BR, Wright LL, Poole WK, McDonald SA. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation between 1993 and 1998. *Pediatrics*. 2005;116(3):635–643
57. Janssen AJWM, Nijhuis-van der Sanden MW, Akkermans RP, Oostendorp RA, Kollée LA. Influence of behaviour and risk factors on motor performance in preterm infants at age 2 to 3 years. *Dev Med Child Neurol*. 2008;50(12):926–931
58. Messinger D, Lambert B, Bauer CR, Bann CM, Hamlin-Smith K, Das A. The relationship between behavior ratings and concurrent and subsequent mental and motor performance in toddlers born at extremely low birth weight. *J Early Interv*. 2010;32(3):214–233
59. Charkaluk ML, Truffert P, Fily A, Ancel PY, Pierrat V, Epipage study group. Neurodevelopment of children born very preterm and free of severe disabilities: the Nord-Pas de Calais Epipage cohort study. *Acta Paediatr*. 2010;99(5):684–689
60. European Union. EU physical activity guidelines: recommended policy actions in support of health-enhancing physical activity. Available at: https://ec.europa.eu/assets/eac/sport/library/policy_documents/eu-physical-activity-guidelines-2008_en.pdf. Accessed June 4, 2021
61. Daugbjerg SB, Kahlmeier S, Racioppi F, et al. Promotion of physical activity in the European region: content analysis of 27 national policy documents. *J Phys Act Health*. 2009;6(6):805–817
62. WHO. Physical activity strategy for the WHO European region 2016-2025. Available at: https://www.euro.who.int/__data/assets/pdf_file/0010/282961/65wd09e_PhysicalActivityStrategy_150474.pdf Accessed June 4, 2021
63. Hills AP, Dengel DR, Lubans DR. Supporting public health priorities: recommendations for physical education and physical activity promotion in schools. *Prog Cardiovasc Dis*. 2015;57(4):368–374
64. Cheung PC, Franks PA, Kramer MR, et al. Elementary school physical activity opportunities and physical fitness of students: a statewide cross-sectional study of schools. *PLoS One*. 2019;14(1):e0210444
65. Yuksel HS, Şahin FN, Maksimovic N, Drid P, Bianco A. School-based intervention programs for preventing obesity and promoting physical activity and fitness: a systematic review. *Int J Environ Res Public Health*. 2020;17(1):347
66. Hernán MA, Hsu J, Healy B. A second chance to get causal inference right: a classification of data science tasks. *Chance*. 2019;32(1):42–49

Chapter 5 – Differences in risk factors for cerebral palsy and non-cerebral palsy movement difficulties among children born extremely preterm

5.1. Preface

Among EPT children, studies report CP prevalence around 10%, whereas for children without CP, we confirmed in the *previous chapter* (study 1) that up to half of them have non-CP motor problems. To pursue the objectives in our first study, of investigating the prevalence of developmental motor problems and their risk factors, we included children with CP in this second study to estimate the prevalence of CP after EPT birth in our European population-based multi-country cohort and to compare the risk profiles for CP and non-CP MD. The analysis of risk factors aims to help health professionals and policy makers identify specific subgroups of children who could benefit from targeted follow-up and early intervention programs. As stated by McIntyre et al. (2011), health professionals need to understand the distinction in clinical risk factors between CP and other motor difficulties in order to propose more effective and early interventions. As mentioned previously, children with CP are excluded from most studies using the MABC-2 or other tools for the measure of motor development, and only one systematic review has examined the factors associated with both CP and non-CP MD in the same study (Linsell et al., 2016).

With our results, we confirmed a prevalence of CP of around 10% and reinforced knowledge on the different clinical risk factors for CP with associations found for severe brain lesions (IVH and cPVL), BPD and other neonatal morbidities, postnatal corticosteroids, confirmed late infection, male sex, low Apgar score and congenital anomalies. We observed both similarities and differences in the risk profiles for CP and non-CP MD. Male sex, BPD and postnatal corticosteroids were associated with both outcomes. However, while severe brain lesions were also risk factors for non-CP MD, the association was of a much lower order of magnitude. GA and SGA were specifically associated with non-CP MD, whereas low Apgar score and congenital anomalies were associated with an increased risk of CP. Last, as hypothesized and even if young maternal age was associated with both outcomes, sociodemographic risk factors were more strongly and consistently associated with non-CP MD compared to CP. These results are useful for identifying children at risk and may also provide insight into discordant time trends in these disorders (declining CP rates and stagnating non-CP MD) since the risk of CP was more strongly associated with medical factors

for which effective evidence-based intervention exist, while non-CP MD were linked to risk factors for which interventions are less effective, e.g., GA, SGA or sociodemographic factors.

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POPULATION STUDY ARTICLE



Risk factors for cerebral palsy and movement difficulties in 5-year-old children born extremely preterm

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BACKGROUND: Motor impairment is common after extremely preterm (EPT, <28 weeks' gestational age (GA)) birth, with cerebral palsy (CP) affecting about 10% of children and non-CP movement difficulties (MD) up to 50%. This study investigated the sociodemographic, perinatal and neonatal risk factors for CP and non-CP MD.

METHODS: Data come from a European population-based cohort of children born EPT in 2011–2012 in 11 countries. We used multinomial logistic regression to assess risk factors for CP and non-CP MD (Movement Assessment Battery for Children – 2nd edition ≤5th percentile) compared to no MD (>15th percentile) among 5-year-old children.

RESULTS: Compared to children without MD ($n = 366$), young maternal age, male sex and bronchopulmonary dysplasia were similarly associated with CP ($n = 100$) and non-CP MD ($n = 224$) with relative risk ratios (RRR) ranging from 2.3 to 3.6. CP was strongly related to severe brain lesions (RRR >10), other neonatal morbidities, congenital anomalies and low Apgar score (RRR: 2.4–3.3), while non-CP MD was associated with primiparity, maternal education, small for GA (RRR: 1.6–2.6) and severe brain lesions, but at a much lower order of magnitude.

CONCLUSION: CP and non-CP MD have different risk factor profiles, with fewer clinical but more sociodemographic risk factors for non-CP MD.

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IMPACT:

- Young maternal age, male sex and bronchopulmonary dysplasia similarly increased risks of both cerebral palsy and non-cerebral palsy movement difficulties.
- Cerebral palsy was strongly related to clinical risk factors including severe brain lesions and other neonatal morbidities, while non-cerebral palsy movement difficulties were more associated with sociodemographic risk factors.
- These results on the similarities and differences in risk profiles of children with cerebral palsy and non-cerebral palsy movement difficulties raise questions for etiological research and provide a basis for improving the identification of children who may benefit from follow-up and early intervention.

INTRODUCTION

Children born extremely preterm (EPT, i.e., <28 weeks' gestational age (GA)) have higher risks of neurodevelopmental problems than children born at term.^{1,2} One well-documented consequence of EPT birth is cerebral palsy (CP), described as “a group of permanent disorders of the development of movement and posture causing limitations to daily activities and attributed to non-progressive disturbances that occurred in the developing fetal or infant brain”.³ It occurs 100 times more often among EPT

than term-born children, with a prevalence around 10% among those born <28 weeks' GA.^{4–8} Motor difficulties in the absence of CP have more recently also been identified as a major sequela of EPT birth.^{9–14} While less severe than CP, these difficulties, caused by “motor deficits in coordination, balance, gross and fine motor control, and visual motor integration”,¹⁵ are more common. MD without CP, experienced in up to 50% of children born EPT,^{9,10,12,16–19} can interfere with other developmental domains and affect the social function and quality of life.²⁰

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Understanding the sociodemographic, perinatal and neonatal factors that are associated with CP and non-CP MD among EPT children is necessary to advise healthcare professionals and caregivers, and to select appropriate early interventions at the individual and population levels.^{11,15,21,22} Intraventricular hemorrhage (IVH) and cystic periventricular leukomalacia (cPVL), male sex, younger GA and postnatal corticosteroids are associated with an increased risk of CP, while the use of antenatal corticosteroids, maternal magnesium sulfate and surfactant have been associated with lower risks.^{4,11,23–26} Associations with other factors such as premature rupture of membranes (PROM), multiple births and neonatal sepsis are less clearly established among EPT children.^{11,21} One outstanding question, given the major role of neurological damage to the brain, is whether sociodemographic factors are associated with the risk for CP. A systematic review on this association highlighted discrepancies in study results, with some finding no association and others a protective effect of higher social status.²⁷

There has been less investigation of the risk profiles of EPT-born children who develop non-CP MD,^{11,14,28} and reviews of this research have identified few consistent early life risk factors, with exceptions being male sex and the degree of prematurity.^{11,28} However, our recent work in a large European cohort showed that risks of MD were related to a wider range of sociodemographic, perinatal and neonatal factors than reported in these mainly smaller studies.¹⁹ Our results suggest a potential for better early identification of children at risk of later non-CP MD.

In this study, our aim was to compare the sociodemographic, perinatal and neonatal risk factors associated with CP and non-CP MD among children born EPT, using as a reference EPT children without MD. To our knowledge, only one systematic review has examined the factors associated with both CP and MD in the same study.¹¹ We sought to investigate perinatal and neonatal factors in the non-CP group, in particular medical risk factors, in order to assess their effect size in comparison with the better-documented associations of these factors, such as IVH and cPVL, for CP.^{11,29} A second objective was to determine whether the sociodemographic factors, identified as risk factors for non-CP MD in our previous study,¹⁹ were associated with the risk of CP.

METHODS

Study design and participants

This study used data from a prospective, population-based cohort of children born before 32 weeks' GA (very preterm, VPT) in 2011–2012 in 19 regions in 11 European countries. This cohort was constituted by the Effective Perinatal Intensive Care in Europe (EPICE) study, with continuing follow-up in the Screening to Improve Health in Very Preterm Infants in Europe (SHIPS) study.³⁰ Data were collected from obstetrical and neonatal records during the neonatal hospitalization and parental questionnaires at 2 and 5 years of age. Because of logistic constraints, only the sub-group of children born EPT, who are most at risk of poor outcomes, had a clinical assessment to evaluate neurocognitive and motor functioning at 5 years of age.

Because the motor evaluation was part of these clinical assessments, our study population was limited to children born EPT who were included in the 5-year follow-up. Among children without CP, those with a severe neurodevelopmental impairment (NDI), defined as an intelligence quotient ≤ 54 (< -3 standard deviation (SD)) or severe hearing or visual impairment, were excluded because of the difficulty of accurately assessing their motor function using standardized tests.³¹

Cerebral palsy diagnosis and classification of movement difficulties

This study compares children with CP and those with non-CP MD to children without MD. CP was defined as a formal clinical diagnosis at 5 years of age, reported by parents in the 5-year parental questionnaire, except in France, where it was recorded during a clinical assessment. For children without CP, MD were assessed using the Movement Assessment Battery for Children – 2nd edition (MABC-2),³¹ a validated and commonly

used test,^{9,32} evaluating motor performance on eight tasks in three domains: manual dexterity, aiming and catching, and balance skills. As detailed elsewhere,^{19,33} the MABC-2 was administered by trained psychologists or physiotherapists in local routine follow-up programs in Belgium, the Netherlands and Sweden, or by the SHIPS research teams in other countries. While it was not possible to carry out inter-rater reliability across countries, a common data collection form was used to standardize procedures and reporting. In addition, training sessions were held locally and an online discussion forum was set up to discuss possible problems emerging during the data collection. The study was undertaken among all children born < 28 weeks' GA and the assessors were not blinded to the child's medical history.

Non-CP MD is defined as an age-adjusted percentile score ≤ 5 th percentile and no MD as > 15 th percentile. Children between the 6th and the 15th percentile are considered at risk of MD and were excluded from this analysis in order to focus on children whose MD status was clearly identified as significantly impaired.³¹ As national norms exist only in Belgium, France, Italy, the Netherlands and the United Kingdom,^{31,34–36} and the use of different MABC-2 norms may have an impact on the classification of MD,³⁷ we applied the United Kingdom norms, originally developed for the test and most commonly used in the literature, to classify MD in all countries.^{31,37}

Children who had missing or incomplete MABC-2 data were reviewed on a case-to-case basis by neurodevelopmental specialists and an epidemiologist (R.C., U.A., S.J., and J.Z.). If a child was unable to complete a task or component because of severe motor impairment, the lowest score was assigned for that task and/or component. If data were missing for a task/component score in the absence of other developmental problems, the average of the other tasks within the component/in total was imputed. In Belgium, some children had percentile scores derived from the administration of the MABC (1st edition) which were used.³⁸ In all other cases, scores were left as missing.

Risk factors

We selected variables hypothesized to be associated with risks of CP or non-CP MD based on biological plausibility and the scientific literature. Sociodemographic factors included maternal age and parity at delivery, parental cohabiting status, maternal educational level,³⁹ household unemployment status, and maternal country of birth. Perinatal factors were GA, small for GA (SGA),⁴⁰ Apgar score < 7 at 5 min, sex, multiple birth, delivery in a level 3 maternity unit, antepartum hemorrhage after week 20, PROM > 12 h, preeclampsia/eclampsia/HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, any antenatal corticosteroids, and congenital anomalies.⁴¹ Lastly, neonatal morbidities or care factors included IVH grade determined using Papile's classification,⁴² cPVL [recorded if cystic abnormalities were present on ultrasound or CT scan], retinopathy of prematurity (ROP) stage III or more, surgical necrotizing enterocolitis (NEC, requiring surgery or peritoneal drainage), presence of bronchopulmonary dysplasia (BPD, defined as supplemental oxygen and/or ventilatory support [continuous positive airway pressure or mechanical ventilation] at 36 weeks' postmenstrual age), receipt of postnatal corticosteroids,⁴³ and presence of confirmed late infection (> 72 h of life).

Some factors, associated with motor impairment in the literature,^{11,14,28,44} could not be included because the information was not systematically collected (intrauterine infection, chorioamnionitis), samples were small (magnesium sulfate administered in only 36 cases) or variables were collinear (mechanical ventilation and BPD). Finally, wide variations in medical practices between the participating countries (e.g., cesarean section)⁴⁵ complicated the interpretation of some interventions.

Statistical analyses

First, we described the sociodemographic and clinical characteristics of the children with no MD, non-CP MD and CP, as well as of children lost to follow-up. We measured the association of sociodemographic, perinatal and neonatal variables with the probability of having non-CP MD or CP compared to children without MD using multinomial logistic regressions, with country modeled as a fixed effect and taking into consideration clustering of multiple pairs. We estimated four models: (1) unadjusted; (2) adjusted for all sociodemographic factors; (3) adjusted for all sociodemographic and perinatal factors; and (4) adjusted for all sociodemographic, perinatal and neonatal factors.

Loss to follow-up and missing data. As done previously for this cohort,^{19,46–48} we used inverse probability weighting (IPW) to take into

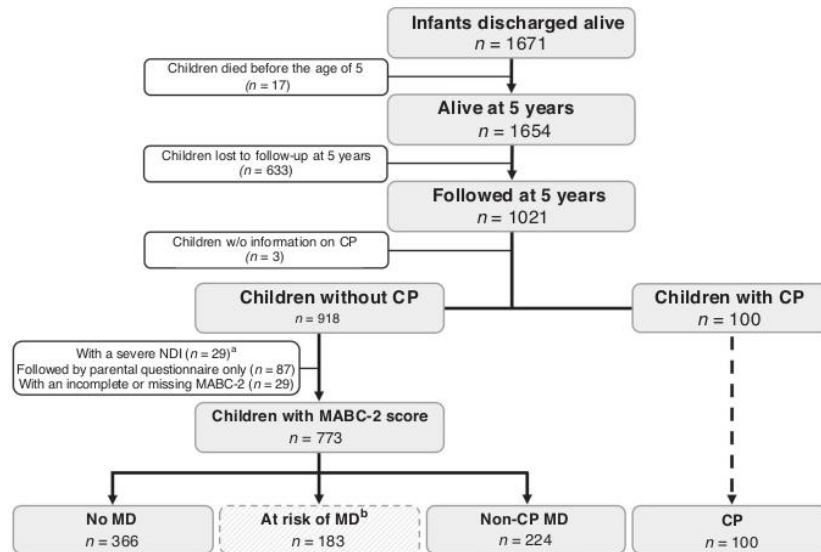


Fig. 1 Flowchart of the study population selection from the SHIPS' cohort (children born <28 weeks' gestational age). w/o without, CP cerebral palsy, NDI neurodevelopmental impairment, MABC-2 Movement Assessment Battery for Children – 2nd edition, MD movement difficulties. No MD (MABC-2 >15th percentile); at risk of MD (6th–15th percentile); non-CP MD (\leq 5th percentile). ^aNeurodevelopmental impairment (NDI) integrated cognitive, hearing and visual impairment. Severe NDI defined as an intelligence quotient (IQ) \leq 54 (<-3 SD), deafness or difficulties hearing even with hearing aids or implants or blindness or seeing light only. ^bChildren between the 6th and the 15th percentile are considered at risk of MD and were excluded from this analysis in order to focus on children whose MD status was clearly identified as significantly impaired.³¹

account loss to follow-up.^{49,50} Characteristics of responders and non-responders potentially affecting loss to follow-up were used to define a weight inversely proportional to the probability of response. Missing data for covariates were imputed using multiple imputation by chained equations for the weights ($m=20$) and for the final models ($m=20$).^{51,52} In the final models, three variables had a percentage of missing data >4.0%: Apgar score (8.4%), household unemployment status (7.1%), and parental cohabiting status (5.4%). Data were assumed to be missing at random after taking into consideration observed covariates. We did not impute data for children with missing MABC-2 scores or CP as the missing at-random assumptions likely did not hold. Final models used IPW and multiple imputation.⁵³

We carried out two sensitivity analyses: rerunning final models using the unweighted and complete case samples and excluding children with severe NDI in the CP group, as this was an exclusion criterion for children without CP. All analyses were carried out using the statistical software Stata version 15.0 (StataCorp, College Station, TX).

RESULTS

In the cohort, 1654 EPT-born infants were alive at 5 years of age and 1021 (61.7%) were followed up (Fig. 1). Children lost to follow-up were more likely to have social risk factors and be SGA (Supplementary Table 1). One hundred children had a CP diagnosis and among children without CP, after exclusions for severe NDI ($n=29$) and missing MABC-2 measures ($n=116$), 224 were classified as having non-CP MD and 366 with no MD.

Among children without MD, 10.3% had a mother aged 25 years or younger, while this proportion was higher among children with non-CP MD (23.0%) and with CP (26.9%) (Table 1). There were more primiparous women in the non-CP MD group, compared to the no MD or CP groups; and 39.9%, 30.7% and 28.6% of the children without MD, non-CP MD, and CP, respectively, had mothers with high educational levels. Among children with CP, over 20% of households had at least one unemployed parent. This proportion was lower among children with non-CP MD (17.2%) and no MD (8.6%). Having GA <26 weeks and male sex was more common in the non-CP MD and CP groups. Neonatal morbidities

were more prevalent in these groups as well, with very high rates of IVH/cPVL among children with CP.

In multinomial models estimating relative risk ratios (RRR) adjusted for sociodemographic and perinatal factors, younger maternal age continued to be associated with both non-CP MD and CP, primiparity with non-CP MD only, while associations for education and household unemployment status were attenuated for the CP group (Table 2). These patterns persisted after including adjustment for neonatal factors; in the fully adjusted model, children with non-European-born mothers were more likely to have non-CP MD, but not CP.

Low GA and male sex were consistently associated with both non-CP MD and CP after adjustment for sociodemographic and perinatal factors, while other perinatal factors had associations with only one of the outcomes: SGA <3rd percentile raised risks of non-CP MD, while Apgar score <7 and congenital anomalies were associated with CP. Outborn birth raised risks of CP only in unadjusted models. Adjustment for neonatal factors mitigated the associations with perinatal risk factors. In this final model, only male sex was associated with both outcomes, GA associated with non-CP MD only and Apgar score <7 and congenital anomalies with CP only.

Most neonatal morbidities were more strongly related to CP than to non-CP MD. Very high and exponentially increasing risks by grade were observed for IVH for CP, whereas for non-CP MD, only IVH grade IV was a strong risk factor. cPVL was associated with both non-CP MD and CP but with a magnitude over 5 times greater for CP. Other morbidities (ROP, NEC, postnatal corticosteroids and confirmed late infection) were associated with CP and not or less associated with non-CP MD. BPD was similarly associated with both non-CP MD and CP. Some of these associations were mitigated in the full model.

Sensitivity analyses on the unweighted and complete case sample (Supplementary Table 3) yielded similar conclusions. After excluding children with severe NDI ($n=20$) in the CP group (Supplementary Table 4) associations with maternal age, ROP and receipt of postnatal corticosteroids were no longer significant, and receipt of antenatal corticosteroids reduced risk of CP.

Table 1. Sample characteristics by motor category among extremely preterm children.

	No MD		Non-CP MD		CP	
	N	%	N	%	N	%
<i>Sociodemographic characteristics</i>						
Maternal age at childbirth (years)						
<25	35	10.3	55	23.0	29	26.9
25–34	200	58.9	126	52.6	58	53.6
≥35	104	30.8	59	24.4	21	19.5
Parental cohabiting status [single/other]	49	14.9	28	13.2	18	16.5
Maternal educational level						
Low education ISCED 0–2	54	16.3	54	23.5	27	25.3
Intermediate education ISCED 3–5	144	43.8	105	45.8	49	46.1
High education ISCED 6–8	131	39.9	70	30.7	31	28.6
Household unemployment status [at least one parent unemployed]	28	8.6	36	17.2	22	21.3
Primiparous (at child's birth)	181	54.2	143	59.8	47	43.5
Country of birth						
Native-born	245	72.8	171	71.4	80	71.4
Other European country	22	6.5	19	7.9	5	4.8
Non-European country	70	20.8	49	20.6	27	23.8
<i>Perinatal characteristics</i>						
GA (weeks)						
≤24	24	7.1	46	19.2	17	15.2
25	48	14.1	53	21.9	24	21.9
26	107	31.6	62	25.8	26	23.7
27	160	47.1	79	33.0	44	39.3
SGA						
<3rd percentile	38	11.2	41	17.1	11	9.6
3rd–9th percentile	28	8.3	22	9.3	7	6.3
≥10th percentile	273	80.5	176	73.7	94	84.0
Apgar less than 7	71	22.2	68	31.4	50	51.4
Male sex	138	40.6	145	60.4	76	68.5
Multiple birth	114	33.7	52	21.8	26	22.9
Delivery in a level 3 maternity unit	300	88.5	205	85.8	83	74.3
Antepartum hemorrhage ^a	81	24.5	77	32.9	38	36.3
PROM	89	26.5	61	25.4	28	25.9
Preeclampsia/eclampsia/HELLP	29	8.7	25	10.4	7	6.5
Antenatal corticosteroids	294	87.2	213	89.4	87	77.7
Congenital anomaly	20	6.0	23	9.8	15	13.4
<i>Neonatal characteristics</i>						
IVH grades						
None	233	69.1	135	57.5	36	33.3
Grade I/II	92	27.2	74	31.6	36	33.3
Grade III	11	3.1	13	5.5	20	18.8
Grade IV	2	0.6	13	5.4	16	14.6
cPVL	9	2.6	14	5.7	24	21.9
ROP stage III or more	18	5.3	44	18.7	20	18.4
Surgical NEC	10	2.8	12	4.8	13	11.8
BPD ^b	78	23.4	120	51.2	55	50.4
Postnatal corticosteroids	71	21.1	97	41.2	49	43.7
Confirmed late infection	167	49.9	134	56.3	78	71.3
<i>Country (region)</i>						
Belgium (Flanders)	18	5.3	12	5.0	15	13.7
Denmark (Eastern Region)	24	7.0	9	3.6	2	1.5

Table 1. continued

	No MD		Non-CP MD		CP	
	N	%	N	%	N	%
Estonia (entire country)	12	3.4	6	2.5	1	1.1
France (Burgundy, Ile-de-France, Northern Region)	83	24.4	15	6.3	22	19.9
Germany (Hesse, Saarland)	37	11.0	24	9.9	17	15.2
Italy (Emilia-Romagna, Lazio, Marche)	38	11.2	34	14.3	13	11.7
The Netherlands (Central Eastern)	26	7.7	6	2.5	2	1.9
Poland (Wielkopolska)	4	1.1	17	7.1	8	6.9
Portugal (Lisbon, Northern Region)	30	9.0	22	9.1	6	5.2
The United Kingdom (East Midlands, Northern, Yorkshire and the Humber)	55	16.1	87	36.3	19	17.1
Sweden (Greater Stockholm)	13	3.9	7	3.1	6	5.7

Values are weighted frequencies (*N*s rounded to a whole number) and percentages (% excluding missing values and rounded to one decimal), all with the use of inverse probability weighting (IPW) to correct loss to follow-up.

MD movement difficulties, CP cerebral palsy, ISCED International Standard Classification of Education,³⁹ GA gestational age, SGA small for gestational age, PROM premature rupture of membranes, HELLP hemolysis, elevated liver enzymes, and low platelets (syndrome), IVH intraventricular hemorrhage, cPVL cystic periventricular leukomalacia, ROP retinopathy of prematurity, NEC necrotizing enterocolitis, BPD bronchopulmonary dysplasia.

^aAntepartum hemorrhage after week 20.

^bDefined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.

DISCUSSION

Summary of main findings

Young maternal age, male sex and BPD similarly increased risks of both CP and non-CP MD, with RRR ranging from 2 to 3 in adjusted models. In contrast, other factors affected risks of these outcomes differently; CP was strongly related to brain lesions (IVH and cPVL), other neonatal morbidities, congenital anomalies and a low Apgar score, while non-CP MD was associated with primiparity, low maternal education and SGA. Children with severe IVH and cPVL also faced greater risks of non-CP MD, but this was at a much lower order of magnitude. GA was related to both outcomes in models adjusted for perinatal factors, but this association did not persist for CP after adjustment for neonatal morbidities.

Perinatal and neonatal risk factors

Our results on perinatal and neonatal risk profiles are in line with known etiological pathways for CP and reinforce our knowledge on non-CP motor impairments. Risks associated with male sex, IVH, cPVL, and BPD have been reported in previous reviews on risk factors for CP and non-CP motor impairment.^{11,14,27,28,44} In contrast, evidence for IVH, cPVL and BPD has been inconsistent for non-CP motor impairment.^{11,14,28} Furthermore, while, cPVL and IVH grade III and IV are the most important predictors of CP in VPT infants,^{11,23,24,54} the evidence concerning lower grade IVH remains limited. We found that all IVH grades, including I and II when combined, were related to CP and RRR increased exponentially with higher grades. Only IVH grade IV was associated with non-CP MD and with a lower RRR than for CP. cPVL was also more strongly associated with CP than with non-CP MD. Other neonatal morbidities had a stronger association with CP, for instance, confirmed late infection, as reported previously,^{44,55,56} or were only associated with CP, as was the case for NEC. In contrast, BPD was associated with non-CP MD and CP with similar RRR.

Other perinatal factors, including GA, SGA, complications of pregnancy and management at birth and during the neonatal hospitalization have been inconsistently associated with CP and non-CP MD. Contrary to patterns observed for non-CP MD, where lower GA remained a risk factor after adjustment for neonatal factors, this association disappeared for CP. This result is concordant with results from 7 of 9 studies included in one review.¹¹ One explanation is that the impact of GA on CP is principally indirect, acting through greater vulnerability to neonatal morbidities,²⁹ whereas for non-CP MD lower GA, even

in the absence of morbidities exerts independent adverse effects.^{8,11,23} We found that pregnancy complications, such as preeclampsia/eclampsia/HELLP syndrome, antepartum hemorrhage and PROM were not associated with either outcome. In contrast, SGA was associated with non-CP MD, while a low Apgar score and congenital anomalies were specifically associated with CP. In their review, Evensen et al.¹⁴ found poor fetal growth to be a risk factor for poor motor outcomes in several studies of children born VPT or very low birth weight (i.e., <1500 g) without CP. A recent study from Italy also found that SGA was a risk factor for non-CP MD.⁵⁷ As SGA is not a risk factor for severe brain lesions,⁵⁸ this may explain the absence of association with CP. Low Apgar score, which can reflect poor adaptation at birth was reported to increase the risk of CP in the systematic review from van Lieshout et al.^{44,59}

In their systematic review, Linsell et al.¹¹ concluded that there was some evidence in VPT/very low birth weight populations that the use of postnatal corticosteroids increased the risk of CP, while the use of antenatal corticosteroids reduced risks. In our study, we observed an association between postnatal corticosteroids and CP, but it was not significant after adjustment for other neonatal factors or after excluding children with severe NDI in the CP group. There was no association between antenatal corticosteroids and CP in the full sample, although a protective association was found in sensitivity analyses excluding children with severe NDI. These varying results might explain inconsistency between studies depending on the inclusion and exclusion criteria. In contrast, postnatal corticosteroids were associated with non-CP MD in all models. A similar association between postnatal corticosteroids and impaired motor outcome was reported in the reviews from Van Hoorn et al.²⁸ and Evensen et al.¹⁴

Sociodemographic factors

Sociodemographic factors appeared to influence risks of non-CP MD more than CP, except for young maternal age which was associated with both in final models. In the literature, associations between sociodemographic factors and non-CP MD have been inconsistent.^{11,14,28} Van Hoorn et al.²⁸ found increased risks in only one of 5 studies, whereas a systematic review on the association between CP and sociodemographic factors reported mixed results, with either no association or a higher risk for children from socially disadvantaged families.²⁷ Solaski et al.²⁷ found low socioeconomic status to be a risk factor for increased CP prevalence in 8 out of

Table 2. Association of sociodemographic, perinatal and neonatal factors with risks of non-CP MD and CP.

	Non-cerebral palsy movement difficulties				Cerebral palsy			
	Unadjusted		Adjusted for all sociodemographic and perinatal factors		Unadjusted		Adjusted for all sociodemographic factors	
	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	Adjusted for all sociodemographic, perinatal and neonatal factors RRR [95% CI]
<i>Sociodemographic factors</i>								
Maternal age at childbirth (years) [25–34 years]								
<25	2.68 [1.36–5.26]	2.27 [1.14–4.55]	2.34 [1.13–4.85]	2.80 [1.25–6.28]	2.72 [1.22–6.09]	2.71 [1.17–6.31]	2.42 [1.06–5.53]	2.67 [1.09–6.55]
≥35	0.95 [0.62–1.46]	1.06 [0.67–1.67]	1.07 [0.65–1.77]	1.08 [0.64–1.82]	0.66 [0.36–1.20]	0.59 [0.31–1.13]	0.64 [0.32–1.27]	0.73 [0.33–1.61]
Parental cohabiting status [married/couple/cohabiting]								
Single/other	0.98 [0.50–1.89]	0.93 [0.45–1.92]	1.06 [0.48–2.33]	1.07 [0.49–2.37]	1.20 [0.59–2.46]	1.21 [0.56–2.58]	1.27 [0.58–2.75]	1.28 [0.57–2.89]
Maternal educational level [high education ISCED 6–8]								
Low education ISCED 0–2	2.84 [1.56–5.19]	2.38 [1.18–4.82]	2.58 [1.20–5.54]	2.07 [0.95–4.53]	2.21 [1.05–4.64]	1.55 [0.67–3.62]	1.50 [0.57–3.93]	1.25 [0.46–3.40]
Intermediate education ISCED 3–5	1.13 [0.70–1.80]	0.98 [0.57–1.68]	1.03 [0.58–1.85]	0.88 [0.48–1.61]	1.24 [0.70–2.20]	0.88 [0.46–1.66]	0.93 [0.47–1.84]	0.67 [0.31–1.45]
Household employment status [parents employed]								
At least one parent unemployed	2.33 [1.08–5.03]	2.40 [1.16–4.97]	2.20 [0.95–5.11]	2.46 [1.02–5.93]	2.68 [1.17–6.14]	2.63 [1.17–5.91]	1.72 [0.67–4.37]	2.09 [0.78–5.62]
Parity [multiparous]								
Primiparous	1.44 [0.95–2.18]	1.60 [1.03–2.49]	1.58 [0.99–2.51]	1.52 [0.92–2.52]	0.71 [0.41–1.23]	0.66 [0.37–1.18]	0.75 [0.42–1.35]	0.64 [0.34–1.22]
Maternal country of birth [native-born]								
Other European country	1.41 [0.66–2.99]	1.21 [0.58–2.54]	1.38 [0.60–3.20]	1.40 [0.58–3.34]	0.75 [0.22–2.51]	0.63 [0.20–1.99]	0.70 [0.21–2.30]	0.69 [0.21–2.24]
Non-European country	1.46 [0.80–2.69]	1.37 [0.74–2.53]	1.62 [0.86–3.05]	1.94 [1.02–3.70]	1.16 [0.57–2.34]	0.91 [0.46–1.80]	1.04 [0.53–2.04]	1.47 [0.70–3.08]
<i>Perinatal factors</i>								
GA (weeks) [27 weeks]								
≤24	3.66 [1.93–6.95]	3.72 [1.96–7.03]	4.11 [2.03–8.32]	2.23 [1.02–4.89]	2.59 [1.11–6.00]	2.43 [1.02–5.77]	2.60 [1.07–6.30]	0.95 [0.28–3.20]
25	2.49 [1.42–4.36]	3.38 [1.91–5.99]	3.66 [1.99–6.73]	2.42 [1.25–4.69]	1.98 [1.01–3.88]	2.39 [1.25–4.60]	2.61 [1.30–5.26]	1.23 [0.55–2.73]
26	1.26 [0.76–2.09]	1.59 [0.92–2.76]	1.73 [0.98–3.04]	1.38 [0.76–2.50]	0.97 [0.47–2.00]	1.15 [0.58–2.28]	1.23 [0.62–2.41]	1.02 [0.50–2.07]
SGA [≥10th percentile]								
<3rd percentile	1.90 [1.12–3.21]	1.80 [1.06–3.08]	2.07 [1.05–4.06]	1.53 [0.76–3.10]	0.82 [0.38–1.76]	0.90 [0.40–2.00]	1.25 [0.45–3.46]	1.18 [0.42–3.26]
3rd–9th percentile	1.11 [0.57–2.17]	1.27 [0.63–2.56]	1.62 [0.74–3.58]	1.53 [0.67–3.49]	0.68 [0.27–1.70]	0.85 [0.33–2.19]	1.23 [0.46–3.33]	1.07 [0.36–3.14]
Apgar <7 [no]								
Yes	1.53 [0.90–2.60]	1.48 [0.88–2.48]	1.32 [0.77–2.27]	1.05 [0.60–1.83]	3.47 [1.89–6.36]	3.05 [1.73–5.37]	2.55 [1.42–4.60]	1.89 [1.01–3.55]
Child sex [female]								
Male	2.42 [1.59–3.70]	2.35 [1.52–3.63]	2.60 [1.64–4.13]	2.34 [1.45–3.79]	3.22 [1.85–5.60]	3.02 [1.74–5.24]	3.04 [1.74–5.33]	3.46 [1.81–6.58]
Multiple birth [singleton]								
Multiple	0.61 [0.38–0.97]	0.72 [0.45–1.14]	0.91 [0.55–1.51]	0.88 [0.51–1.51]	0.60 [0.32–1.13]	0.73 [0.40–1.33]	0.99 [0.54–1.83]	0.73 [0.36–1.45]
Delivery in a level 3 maternity unit [yes]								
No	1.01 [0.56–1.83]	0.87 [0.46–1.64]	0.92 [0.45–1.91]	0.86 [0.41–1.78]	2.43 [1.20–4.92]	1.89 [0.94–3.77]	1.68 [0.75–3.76]	1.41 [0.64–3.10]

Table 2. continued

	Non-cerebral palsy movement difficulties						Cerebral palsy			
	Unadjusted		Adjusted for all sociodemographic and perinatal factors		Adjusted for all sociodemographic and perinatal factors		Unadjusted		Adjusted for all sociodemographic factors	Adjusted for all sociodemographic and perinatal factors
	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]
Antepartum hemorrhage after week 20 [no]										
Yes	1.37 [0.83–2.24]	1.35 [0.81–2.26]	1.16 [0.68–2.01]	1.32 [0.74–2.34]	1.78 [0.97–3.27]	1.75 [0.97–3.15]	1.25 [0.67–2.36]	0.86 [0.39–1.89]		
PROM [no]										
Yes	1.00 [0.62–1.60]	1.06 [0.65–1.72]	1.00 [0.58–1.71]	0.85 [0.49–1.49]	0.98 [0.54–1.77]	0.94 [0.51–1.75]	0.97 [0.49–1.91]	0.68 [0.34–1.38]		
Preeclampsia/eclampsia/HELLP [no]										
Yes	1.53 [0.85–2.74]	1.56 [0.84–2.88]	1.37 [0.63–2.94]	1.02 [0.42–2.46]	0.77 [0.33–1.76]	0.91 [0.38–2.18]	1.09 [0.37–3.24]	0.64 [0.19–2.20]		
Antenatal corticosteroids [yes]										
No	0.80 [0.38–1.69]	0.68 [0.32–1.43]	0.81 [0.35–1.90]	0.64 [0.27–1.53]	1.75 [0.85–3.57]	1.37 [0.68–2.77]	1.29 [0.57–2.90]	1.02 [0.43–2.42]		
Congenital anomaly [no]										
Yes	1.76 [0.77–4.00]	1.58 [0.71–3.51]	1.66 [0.71–3.86]	1.72 [0.67–4.38]	2.40 [0.89–6.49]	2.46 [0.96–6.33]	2.85 [1.02–7.97]	1.90 [0.67–5.37]		
Neonatal factors										
IVH grades [none]										
Grade I/II	1.83 [1.18–2.85]	1.87 [1.19–2.92]	1.55 [0.97–2.47]	1.45 [0.89–2.37]	3.07 [1.54–6.13]	3.65 [1.80–7.39]	3.13 [1.48–6.62]	2.25 [1.08–4.70]		
Grade III	1.81 [0.73–4.48]	1.80 [0.73–4.47]	1.20 [0.48–2.98]	1.08 [0.43–2.74]	15.08 [5.83–39.04]	16.01 [6.37–40.28]	12.40 [4.63–33.20]	10.05 [3.74–26.97]		
Grade IV	11.80 [3.16–44.07]	12.21 [3.47–42.95]	9.35 [2.71–32.26]	9.99 [2.15–46.37]	85.07 [19.84–364.75]	93.26 [23.29–373.53]	78.70 [19.91–311.18]	61.35 [9.02–417.43]		
cPVL [no]										
Yes	2.47 [0.99–6.17]	2.40 [1.00–5.73]	2.52 [1.09–5.83]	2.44 [1.03–5.78]	14.95 [5.71–39.13]	14.58 [5.94–35.79]	19.09 [8.25–44.16]	16.34 [5.32–50.18]		
ROP [no]										
Yes	3.29 [1.70–6.35]	2.71 [1.42–5.17]	1.86 [0.94–3.67]	1.43 [0.71–2.88]	3.83 [1.66–8.84]	3.18 [1.37–7.40]	2.46 [0.98–6.17]	1.51 [0.51–4.47]		
NEC [no]										
Yes	1.31 [0.40–4.35]	1.25 [0.43–3.65]	1.36 [0.55–3.40]	1.32 [0.50–3.49]	4.07 [1.21–13.67]	3.31 [1.09–10.04]	3.29 [1.17–9.26]	2.03 [0.55–7.53]		
BPD ^a [no]										
Yes	3.21 [2.07–4.99]	3.70 [2.35–5.82]	2.62 [1.58–4.34]	2.45 [1.42–4.25]	4.11 [2.28–7.42]	4.58 [2.59–8.10]	3.64 [1.92–6.87]	3.08 [1.51–6.29]		
Postnatal corticosteroids [no]										
Yes	3.24 [2.05–5.10]	3.30 [2.03–5.36]	2.39 [1.41–4.05]	1.85 [1.05–3.25]	2.65 [1.50–4.69]	2.87 [1.67–4.92]	2.38 [1.31–4.32]	1.37 [0.71–2.66]		
Confirmed late infection [no]										
Yes	1.45 [0.96–2.21]	1.42 [0.93–2.19]	1.06 [0.64–1.74]	0.90 [0.53–1.54]	3.08 [1.68–5.66]	2.87 [1.60–5.14]	2.48 [1.30–4.72]	2.16 [1.10–4.23]		

Values are relative risk ratios and their 95% confidence intervals (RRR [95% CI]) of having non-CP MD or CP compared to children without MD using multinomial logistic regression models: (1) unadjusted; (2) adjusted for all sociodemographic factors; (3) adjusted for all sociodemographic and perinatal factors; and (4) adjusted for all sociodemographic, perinatal and neonatal factors; all taking into consideration clustering within multiple pairs, with country modeled as a fixed effect, and with the use of inverse probability weighting (IPW) to take into account loss to follow-up and multiple imputed dataset.

CP cerebral palsy, MD movement difficulties, RRR relative risk ratio, CI confidence interval, ISCED International Standard Classification of Education,³⁹ GA gestational age, SGA small for gestational age, PROM premature rupture of membranes, HELLP hemolysis, elevated liver enzymes, and low platelets (syndrome), IVH intraventricular hemorrhage, cPVL cystic periventricular leukomalacia, ROP retinopathy of prematurity, NEC necrotizing enterocolitis, BPD bronchopulmonary dysplasia.

^aDefined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.

the 12 studies included. In another systematic review on prognostic factors for both CP and non-CP motor impairment in children born VPT,¹¹ only 2 out of 12 studies reported an association between sociodemographic factors and a higher risk of CP, namely lower maternal education and African-American origin (study in the United States).

In the literature on non-CP motor impairment,¹¹ lower parental occupation and lower maternal education were associated with motor impairment before 5 years of age.^{11,60,61} However, when restricted to the studies with motor impairment assessed at an older age (≥ 5 years of age) and among children free of major disabilities, none (out of 7 studies) reported an association between non-CP MD and a sociodemographic factor. In another review, on long-term motor outcomes, one article reported an association with both lower maternal age and the mother being unemployed.^{14,62} Young maternal age can be a marker for low social status, but may also reflect other characteristics of the preterm birth as younger mothers are more likely to have spontaneous preterm deliveries and less likely to have vascular complications.

Interpretation for understanding etiology and prevention

We observed similarities in some risk factors for non-CP MD and CP, but risk factor profiles remained different and are indicative of the distinct etiologies of non-CP MD and CP. Comparing these risk profiles can provide insight into why CP rates are declining,^{63,64} given the decreasing prevalence of severe brain lesions and neonatal morbidities, whereas rates of non-CP MD are stagnating or increasing.^{13,65} For non-CP MD, the prevalence of the major clinical risk factors, such as low GA and BPD, is not decreasing and the role of social factors in determining risk requires more comprehensive intervention beyond improvement in neonatal care. To understand these trends, a further question is whether children who may previously have developed CP have shifted to the non-CP MD group. Some researchers have posited a possible continuum between CP and non-CP MD,⁶⁶ with minor neuromotor dysfunction in posture, muscle tone and movement function, which could be defined as complex minor neurological dysfunction and regarded as a borderline form of CP.⁶⁷ Ongoing research in children with non-CP MD that explores brain abnormalities and neurodevelopmental pathways, particularly white matter injury, and corticospinal tract microstructure, both strongly associated with CP, could improve understanding of this question.^{68,69}

Our results add to knowledge for the development and validation of risk prediction models for routine care and intervention.⁷⁰ Recent research, including from this cohort,^{33,71} shows that a substantial proportion of children with non-CP MD are not receiving support services, raising questions about whether these difficulties are detected in routine follow-up. Early interventions to improve motor function in children born preterm and/or with motor difficulties have been found to be beneficial and therefore being able to identify children at risk using sociodemographic, perinatal and neonatal risk profiles has the potential to improve long-term motor outcomes.^{72–75} Better prediction models can also ensure that targeted support is provided to children and their families.

Strengths and limitations

This population-based European multi-regional cohort with a sample of >850 EPT children and standardized data collection on a wide array of risk factors and motor status is one of the largest cohorts with information on this topic. Another strength is the use of the MABC-2 which is a validated measure of MD,^{9,32} including in this high-risk population.⁷⁶ Although test and examiner reliabilities across sites were not assessed, the MABC-2 is considered to have good to excellent inter-rater reliability and test-retest reliability.³² Furthermore, the assessors were not blinded to the child's EPT status as there was no control group and some assessments were

organized within local routine follow-up programs. While this could lead to some bias, there are detailed instructions for administration and objective criteria for the interpretation of the MABC-2 tasks.³¹ Another limitation is the reliance on a parent-reported CP diagnosis, which may lead to some misclassification although most affected children will have a diagnosis by 5 years of age in cohorts with high health service use, such as ours.^{21,77,78} However, information on CP type and severity was not available for analysis.^{79,80} A final limitation relates to possible bias from loss to follow-up which was mainly related to social disadvantage. We used IPW to correct for attrition using information from the full sample at baseline.

CONCLUSION

Based on a large population-based sample of 5-year-old children born EPT in Europe, we identified similarities and differences in the risk profiles of children with CP and non-CP MD. These results raise questions for research on etiology and provide a basis for improving the identification of children who may benefit from follow-up and early intervention. Associations of multiple socio-demographic factors, mainly with non-CP MD, illustrate the importance of considering the social context of intervention programs for children born EPT.

DATA AVAILABILITY

The datasets analyzed during the current study are not publicly available due to health data protection but are available from the corresponding author on reasonable request.

REFERENCES

- Moreira, R. S., Magalhães, L. C. & Alves, C. R. L. Effect of preterm birth on motor development, behavior, and school performance of school-age children: a systematic review. *J. Pediatr. (Rio J.)* **90**, 119–134 (2014).
- Allotey, J. et al. Cognitive, motor, behavioural and academic performances of children born preterm: a meta-analysis and systematic review involving 64 061 children. *BJOG Int. J. Obstet. Gynaecol.* **125**, 16–25 (2018).
- Rosenbaum, P. et al. A report: the definition and classification of cerebral palsy April 2006. *Dev. Med. Child Neurol. Suppl.* **109**, 8–14 (2007).
- O'Shea, T. M. Diagnosis, treatment, and prevention of cerebral palsy. *Clin. Obstet. Gynecol.* **51**, 816–828 (2008).
- Himpens, E., Van den Broeck, C., Oostra, A., Calders, P. & Vanhaesebrouck, P. Prevalence, type, distribution, and severity of cerebral palsy in relation to gestational age: a meta-analytic review. *Dev. Med. Child Neurol.* **50**, 334–340 (2008).
- Hafström, M. et al. Cerebral palsy in extremely preterm infants. *Pediatrics* **141**, e20171433 (2018).
- Adams-Chapman, I. et al. Neurodevelopmental impairment among extremely preterm infants in the neonatal research network. *Pediatrics* **141**, e20173091 (2018).
- Korzeniewski, S. J., Slaughter, J., Lenski, M., Haak, P. & Paneth, N. The complex aetiology of cerebral palsy. *Nat. Rev. Neurol.* **14**, 528–543 (2018).
- de Kieviet, J. F., Piek, J. P., Aarnoudse-Moens, C. S. & Oosterlaan, J. Motor development in very preterm and very low-birth-weight children from birth to adolescence: a meta-analysis. *JAMA* **302**, 2235–2242 (2009).
- Williams, J., Lee, K. J. & Anderson, P. J. Prevalence of motor-skill impairment in preterm children who do not develop cerebral palsy: a systematic review. *Dev. Med. Child Neurol.* **52**, 232–237 (2010).
- Linsell, L., Malouf, R., Morris, J., Kurinczuk, J. J. & Marlow, N. Prognostic factors for cerebral palsy and motor impairment in children born very preterm or very low birthweight: a systematic review. *Dev. Med. Child Neurol.* **58**, 554–569 (2016).
- 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.* **172**, 765–774 (2018).
- Spittle, A. J., Cameron, K., Doyle, L. W., Cheong, J. L., & Victorian Infant Collaborative Study Group. Motor impairment trends in extremely preterm children: 1991–2005. *Pediatrics* **141**, e20173410 (2018).
- Evensen, K. A. I., Ustad, T., Tikanmäki, M., Haaramo, P. & Kajantie, E. Long-term motor outcomes of very preterm and/or very low birth weight individuals

- without cerebral palsy: a review of the current evidence. *Semin. Fetal Neonatal Med.* **25**, 101116 (2020).
15. Spittle, A. J. & Orton, J. Cerebral palsy and developmental coordination disorder in children born preterm. *Semin. Fetal Neonatal Med.* **19**, 84–89 (2014).
 16. Edwards, J. et al. Developmental coordination disorder in school-aged children born very preterm and/or at very low birth weight: a systematic review. *J. Dev. Behav. Pediatr.* **32**, 678–687 (2011).
 17. Bos, A. F., Van Braeckel, K. N. J. A., Hitzert, M. M., Tanis, J. C. & Roze, E. Development of fine motor skills in preterm infants. *Dev. Med. Child Neurol.* **55**(Suppl 4), 1–4 (2013).
 18. Spittle, A. J. et al. Rates of developmental coordination disorder in children born very preterm. *J. Pediatr.* **231**, 61–67.e2 (2021).
 19. Aubert, A. M. et al. Movement difficulties at age five among extremely preterm infants. *Pediatrics* **149**, e2021054920. <https://doi.org/10.1542/peds.2021-054920> (2022).
 20. Zwicker, J. G., Harris, S. R. & Klassen, A. F. Quality of life domains affected in children with developmental coordination disorder: a systematic review. *Child Care Health Dev.* **39**, 562–580 (2013).
 21. McIntyre, S., Morgan, C., Walker, K. & Novak, I. Cerebral palsy—don't delay. *Dev. Disabil. Res. Rev.* **17**, 114–129 (2011).
 22. Zeitlin, J. et al. Priorities for collaborative research using very preterm birth cohorts. *Arch. Dis. Child. Fetal Neonatal Ed.* **105**, 538–544 (2020).
 23. Beaino, G. et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev. Med. Child Neurol.* **52**, e119–e125 (2010).
 24. Himpens, E. et al. Predictability of cerebral palsy and its characteristics through neonatal cranial ultrasound in a high-risk NICU population. *Eur. J. Pediatr.* **169**, 1213–1219 (2010).
 25. Patel, R. M. Short- and long-term outcomes for extremely preterm infants. *Am. J. Perinatol.* **33**, 318–328 (2016).
 26. Ream, M. A. & Lehwald, L. Neurologic consequences of preterm birth. *Curr. Neurol. Neurosci. Rep.* **18**, 48 (2018).
 27. Solaski, M., Majnemer, A. & Oskoui, M. Contribution of socio-economic status on the prevalence of cerebral palsy: a systematic search and review. *Dev. Med. Child Neurol.* **56**, 1043–1051 (2014).
 28. van Hoorn, J. F. et al. Risk factors in early life for developmental coordination disorder: a scoping review. *Dev. Med. Child Neurol.* **63**, 511–519 (2021).
 29. Chen, R. et al. Impact of gestational age on risk of cerebral palsy: unravelling the role of neonatal morbidity. *Int. J. Epidemiol.* **50**, 1852–1863 (2022).
 30. Zeitlin, J. et al. Cohort profile: Effective Perinatal Intensive Care in Europe (EPICE) very preterm birth cohort. *Int. J. Epidemiol.* **49**, 372–386 (2020).
 31. Henderson, S. E., Sugden, D. A. & Barnett, A. L. *Movement Assessment Battery for Children-2* 2nd edn. (Psychological corporation, London, United Kingdom, 2007).
 32. Blank, R. et al. International clinical practice recommendations on the definition, diagnosis, assessment, intervention, and psychosocial aspects of developmental coordination disorder. *Dev. Med. Child Neurol.* **61**, 242–285 (2019).
 33. Costa, R. et al. Motor-related health care for 5-year-old children born extremely preterm with movement impairments. *Dev. Med. Child Neurol.* **64**, 1131–1144. <https://doi.org/10.1111/dmcn.15202> (2022).
 34. Smits-Engelsman, B. *Movement Assessment Battery for Children-2, Dutch Adaptation* 2nd edn. (Pearson Assessment, Amsterdam, The Netherlands, 2010).
 35. Marquet-Doléac, J., Soppelsa, R. & Albaret, J.-M. *Movement Assessment Battery for Children-2, French Adaptation* 2nd edn., Pearson France-ECPA, France, (2016).
 36. Biancotto, M., Borean, M., Bravar, L., Pelamatti, G. M. & Zoia, S. *Movement Assessment Battery for Children-2, Italian Adaptation* 2nd edn. (Giunti O.S., Prato, 2013).
 37. Costa, R. et al. The impact of choice of norms on classification of motor impairment for children born very preterm. *Early Hum. Dev.* **146**, 105056. <https://doi.org/10.1016/j.earlhumdev.2020.105056> (2020).
 38. Henderson, S. E. & Sugden, D. A. *Movement Assessment Battery for Children*. (Psychological corporation, London, United Kingdom, 1992).
 39. UNESCO Institute for Statistics. *International Standard Classification of Education: ISCED 2011* (UNESCO Institute for Statistics, 2012).
 40. Zeitlin, J. et al. Variation in term birthweight across European countries affects the prevalence of small for gestational age among very preterm infants. *Acta Paediatr. Oslo Nor.* **106**, 1447–1455 (2017). 1992.
 41. Draper, E. S. et al. Variability in very preterm stillbirth and in-hospital mortality across Europe. *Pediatrics* **139**, e20161990 (2017).
 42. Papile, L. A., Burstein, J., Burstein, R. & Koffler, H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J. Pediatr.* **92**, 529–534 (1978).
 43. Nuytten, A. et al. Evidence-based neonatal unit practices and determinants of postnatal corticosteroid-use in preterm births below 30 weeks GA in Europe. A population-based cohort study. *PLoS One* **12**, e0170234 (2017).
 44. van Lieshout, P., Candundo, H., Martino, R., Shin, S. & Barakat-Haddad, C. Onset factors in cerebral palsy: a systematic review. *Neurotoxicology* **61**, 47–53 (2017).
 45. Wolf, H. T. et al. Mode of delivery and adverse short- and long-term outcomes in vertex-presenting very preterm born infants: a European population-based prospective cohort study. *J. Perinat. Med.* **49**, 923–931 (2021).
 46. Bonnet, C. et al. Low breastfeeding continuation to 6 months for very preterm infants: a European multiregional cohort study. *Matern. Child. Nutr.* **15**, e12657 (2019).
 47. Seppänen, A.-V. et al. Parents' ratings of post-discharge healthcare for their children born very preterm and their suggestions for improvement: a European cohort study. *Pediatr. Res.* **89**, 1004–1012 (2021).
 48. Piedvache, A. et al. Strategies for assessing the impact of loss to follow-up on estimates of neurodevelopmental impairment in a very preterm cohort at 2 years of age. *BMC Med. Res. Methodol.* **21**, 118 (2021).
 49. Hernán, M. A. & Robins, J. M. Estimating causal effects from epidemiological data. *J. Epidemiol. Community Health* **60**, 578–586 (2006).
 50. Seaman, S. R. & White, I. R. Review of inverse probability weighting for dealing with missing data. *Stat. Methods Med. Res.* **22**, 278–295 (2013).
 51. Royston, P. & White, I. R. Multiple Imputation by Chained Equations (MICE): implementation in Stata. *J. Stat. Softw.* **45**, 1–20 (2011).
 52. White, I. R., Royston, P. & Wood, A. M. Multiple imputation using chained equations: issues and guidance for practice. *Stat. Med.* **30**, 377–399 (2011).
 53. Seaman, S. R., White, I. R., Copas, A. J. & Li, L. Combining multiple imputation and inverse-probability weighting. *Biometrics* **68**, 129–137 (2012).
 54. Tran, U., Gray, P. H. & O'Callaghan, M. J. Neonatal antecedents for cerebral palsy in extremely preterm babies and interaction with maternal factors. *Early Hum. Dev.* **81**, 555–561 (2005).
 55. Mitha, A. et al. Neonatal infection and 5-year neurodevelopmental outcome of very preterm infants. *Pediatrics* **132**, e372–e380 (2013).
 56. Rogers, E. E. & Hintz, S. R. Early neurodevelopmental outcomes of extremely preterm infants. *Semin. Perinatol.* **40**, 497–509 (2016).
 57. Zoia, S. et al. Early factors associated with risk of developmental coordination disorder in very preterm children: a prospective area-based cohort study in Italy. *Paediatr. Perinat. Epidemiol.* **36**, 683–695 (2022).
 58. Zeitlin, J. et al. Impact of fetal growth restriction on mortality and morbidity in a very preterm birth cohort. *J. Pediatr.* **157**, 733–739.e1 (2010).
 59. Himmelmann, K., Ahlin, K., Jacobsson, B., Cans, C. & Thorsen, P. Risk factors for cerebral palsy in children born at term. *Acta Obstet. Gynecol. Scand.* **90**, 1070–1081 (2011).
 60. Charkaluk, M. L. et al. Neurodevelopment of children born very preterm and free of severe disabilities: the Nord-Pas de Calais Epipage cohort study. *Acta Paediatr. Oslo Nor.* **99**, 684–689 (2010).
 61. Janssen, A. J. W. M., der Sanden, M. W. G. N., Akkermans, R. P., Oostendorp, R. A. B. & Kollée, L. A. A. Influence of behaviour and risk factors on motor performance in preterm infants at age 2 to 3 years. *Dev. Med. Child Neurol.* **50**, 926–931 (2008).
 62. Moreira, R. S., Magalhães, L. C., Dourado, J. S., Lemos, S. M. A. & Alves, C. R. L. Factors influencing the motor development of prematurely born school-aged children in Brazil. *Res. Dev. Disabil.* **35**, 1941–1951 (2014).
 63. Platt, M. J. 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 Lond. Engl.* **369**, 43–50 (2007).
 64. Smithers-Sheedy, H. et al. Declining trends in birth prevalence and severity of singletons with cerebral palsy of prenatal or perinatal origin in Australia: a population-based observational study. *Dev. Med. Child Neurol.* **64**, 1114–1122 (2022).
 65. Cheong, J. L. et al. Temporal trends in neurodevelopmental outcomes to 2 years after extremely preterm birth. *JAMA Pediatr.* **175**, 1035–1042. <https://doi.org/10.1001/jamapediatrics.2021.2052> (2021).
 66. Pearsall-Jones, J. G., Piek, J. P. & Levy, F. Developmental coordination disorder and cerebral palsy: categories or a continuum? *Hum. Mov. Sci.* **29**, 787–798 (2010).
 67. Ferrari, F. et al. Preterm birth and developmental problems in the preschool age. Part I: minor motor problems. *J. Matern. Fetal Neonatal Med.* **25**, 2154–2159 (2012).
 68. Kelly, C. E. et al. Brain structural and microstructural alterations associated with cerebral palsy and motor impairments in adolescents born extremely preterm and/or extremely low birthweight. *Dev. Med. Child Neurol.* **57**, 1168–1175 (2015).
 69. Spittle, A. J. et al. Neonatal white matter abnormality predicts childhood motor impairment in very preterm children. *Dev. Med. Child Neurol.* **53**, 1000–1006 (2011).
 70. Hernán, M. A., Hsu, J. & Healy, B. A second chance to get causal inference right: a classification of data science tasks. *CHANCE* **32**, 42–49 (2019).
 71. Pierrat, V. et al. Neurodevelopmental outcomes at age 5 among children born preterm: EPIPAGE-2 cohort study. *BMJ* **373**, n741 (2021).
 72. Doyle, L. W. et al. Long term follow up of high risk children: who, why and how? *BMC Pediatr.* **14**, 279 (2014).

73. Spittle, A. J., Orton, J., Anderson, P. J., Boyd, R. & Doyle, L. W. Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. *Cochrane Database Syst. Rev.* **2015**, CD005495. <https://doi.org/10.1002/14651858.CD005495.pub4> (2015).
74. Smits-Engelsman, B. et al. Efficacy of interventions to improve motor performance in children with developmental coordination disorder: a combined systematic review and meta-analysis. *Dev. Med. Child Neurol.* **55**, 229–237 (2013).
75. Harris, S. R., Mickelson, E. C. R. & Zwicker, J. G. Diagnosis and management of developmental coordination disorder. *CMAJ* **187**, 659–665 (2015).
76. Dewey, D. et al. Assessment of developmental coordination disorder in children born with extremely low birth weights. *Dev. Neuropsychol.* **36**, 42–56 (2011).
77. Gorter, J. W., Ketelaar, M., Rosenbaum, P., Hadders, P. J. M. & Palisano, R. Use of the GMFCS in infants with CP: the need for reclassification at age 2 years or older. *Dev. Med. Child Neurol.* **51**, 46–52 (2009).
78. Seppänen, A.-V. et al. High healthcare use at age 5 years in a European cohort of children born very preterm. *J. Pediatr.* **243**, 69–77.e9 (2022).
79. Palisano, R. et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev. Med. Child Neurol.* **39**, 214–223 (1997).
80. Demešić Drljan, Č. et al. Cerebral palsy in preterm infants. *Vojnosanit. Pregl.* **73**, 343–348 (2016).

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R.C., S.J., U.A., M.C., C.K.-E., J.L., H.V., M.Z., V.P., J.Z., and the SHIPS Research group made substantial contributions to the conception and design and acquisition of data. A.M.A. and J.Z. analyzed the data. A.M.A., R.C., S.J., U.A., M.C., C.K.-E., J.L., H.V., M.Z., V.P., and J.Z. contributed to the interpretation of data, drafting the article, revising it critically for important intellectual content, and approved the final version to be published. Members of the SHIPS research group approved the final version to be published.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All study regions obtained ethical approval according to national legislation. The study was also approved by the French Advisory Committee on Use of Health Data in Medical Research (CCTIRS) and the French National Commission for Data Protection and Liberties (CNIL). Parents gave their written informed consent to participate in the study prior to any data collection.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41390-022-02437-6>.

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Chapter 6 – Motor-related health care services use among extremely preterm children with movement difficulties

6.1. Preface

In light of the very high prevalence of developmental motor problems among children born EPT, and the potential effectiveness of interventions to improve motor performance in children with CP and non-CP MD, understanding healthcare service use among EPT children with motor difficulties is important. Children born EPT are a clearly identifiable high-risk group for whom more structured and specialised follow-up programmes are warranted. However, whereas international guidelines for health care provision exist for children with a CP diagnosis, this was not the case until recently for EPT children without a formal diagnosis of impairment. Furthermore, non-CP MD such as DCD may be unrecognised by health care professionals. Given the lack of research on health service use among EPT children with developmental motor problems, we aimed to estimate the proportion of EPT children with CP and non-CP MD receiving MRHC services, as well as to describe the factors associated with receiving health care in our cohort.

We found that only 42.8% of children with significant MD and 25.9% of children at risk of MD received MRHC services over the past year, with large differences between countries. In contrast, and reassuringly, almost 90% of children with a CP diagnosis were receiving MRHC services at five years of age, with consistent results for the countries. The co-occurrence of MD with other developmental difficulties was a factor associated with a higher use of services. Children with a mother born outside of Europe were less likely to receive MRHC services, whereas unemployment in the household, severe neonatal morbidity, and receipt of other healthcare supports were associated with receiving MRHC.

These results provide support for the establishment of international guidelines for the detection and support of children with motor problems during the first years of life since motor problems may sometimes become apparent only at school-age. Our results also suggest that healthcare professionals, who are more familiar with ADHD and learning disabilities, may underrecognise non-CP MD. Better training of healthcare professionals may therefore improve both detection and management of MD. Finally, some parents may not be aware of their child's difficulty or consider that it could benefit from care.

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ORIGINAL ARTICLE

Motor-related health care for 5-year-old children born extremely preterm with movement impairments

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Abstract

Aim: To (1) determine the proportion of 5-year-old children born extremely preterm (EPT) with movement difficulties including cerebral palsy (CP) and the proportion of these children receiving motor-related health care (MRHC), and (2) describe factors associated with receiving MRHC.

Method: Children born before 28 weeks' gestation in 2011 to 2012 in 11 European countries were assessed with the Movement Assessment Battery for Children, Second Edition (MABC-2) at 5 years of age. Information on family characteristics, child health including CP diagnosis, and health care use were collected using parent-report questionnaires. MRHC was defined as visits in the previous year with health care providers (physical and occupational therapists) specialized in assessing/treating motor problems. We analysed receipt of MRHC and associated factors among children at risk of movement difficulties (MABC-2 score 6th–15th centiles), with significant movement difficulties (SMD; ≤5th centile) or with CP.

Results: Of 807 children assessed at 5 years 7 months (SD 4 months; 4 years 7 months–7 years 1 month), 412 were males (51.1%), 170 (21.1%) were at risk of

Abbreviations: EPT, extremely preterm; ISCED, International Standard Classification of Education; MABC-2, Movement Assessment Battery for Children, Second Edition; MRHC, motor-related health care; SHIPS, Screening to improve Health In very Preterm infantS in Europe; SMD, significant movement difficulties.

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movement difficulties, 201 (24.9%) had SMD, and 92 (11.4%) had CP. Those who received MRHC comprised 89.1% of children with CP, 42.8% with SMD, and 25.9% at risk of movement difficulties. MRHC for children with SMD varied from 23.3% to 66.7% between countries. Children were more likely to receive MRHC if they had other developmental problems or socioemotional, conduct, or attention difficulties.

Interpretation: Efforts are needed to increase MRHC for 5-year-old children born EPT with movement difficulties.

Movement difficulties are a frequent complication after extremely preterm (EPT) birth, before 28 weeks gestational age, and include cerebral palsy (CP), developmental coordination disorder, and other movement difficulties.¹ Together, movement difficulties affect about one-third of 5-year-old children born EPT.^{2,3} Comorbidity with other developmental problems is common.⁴⁻⁷

Motor development implies the reorganization of the neural connections required for the acquisition of skilled movement control in the postnatal period.^{8,9} Early instigation of motor-related health care (MRHC) is important to take advantage of the developing brain's greater neuroplasticity and ability to reorganize neural connectivity in response to new experiences or training during this period.¹⁰ European standards of care for infants born very preterm recommend assessment of motor development in the first years,¹¹ and studies show that interventions to prevent motor impairment and to improve motor performance in children born preterm are beneficial.^{12,13}

However, there is sparse information on the contacts that children born EPT with movement difficulties have with health care providers. This study aimed to determine the proportion of children born EPT with movement difficulties or CP who received MRHC at 5 years of age, as well as the factors related to receiving MRHC in a prospective European birth cohort. We hypothesized that many children born EPT with movement difficulties would receive multidisciplinary care¹⁴ because of the co-occurrence of movement difficulties with other developmental difficulties and that MRHC use would vary across countries, given differences in routine health care follow-up and specialist use.¹⁵⁻¹⁷

METHOD

Study design

Data are from the Screening to improve Health In very Preterm infantS in Europe (SHIPS) project, which followed up the Effective Perinatal Intensive Care in Europe population-based cohort of children born very preterm (<32 weeks gestational age) at 5 years of age.¹⁸ This cohort included all very preterm births over a 12-month period (except in France where it was 6 months) in 2011 to 2012 from 19 regions in 11 European countries.¹⁸ In this cohort, 6792 infants (1671 EPT) survived to discharge from neonatal care.

What this paper adds

- Children born extremely preterm without cerebral palsy frequently experienced motor difficulties.
- Most of these children were not receiving motor-related health care (MRHC).
- Large geographical differences throughout Europe were observed in receipt of MRHC.
- Socioemotional problems were related to MRHC use.

Ethical authorizations from local regional or hospital ethics boards were received, as required by national legislation, and written parental consent was obtained for follow-up. The European SHIPS study was approved by the French Advisory Committee on Use of Health Data in Medical Research and the French National Commission for Data Protection and Liberties.

Study population

Of children born EPT in the cohort who survived to discharge from neonatal care, 17 died between discharge and 5 years (Figure S1). At 5 years, 1021 children were followed up (61.7% participation rate, from 38.7% for the UK to 100% for Estonia). The study population included children born EPT ($n = 807$), either with a diagnosis of CP ($n = 92$; CP defined as having a formal clinical diagnosis as reported by parents or diagnosed by a doctor) or without a diagnosis of CP and a valid motor assessment ($n = 715$) and no severe neurodevelopmental impairment (i.e. deafness or difficulties hearing even with hearing aid or implant; blindness or seeing light only; an IQ score below 55 points [<-3 SD]), and with information on health care service use.

Perinatal data collection

Data on maternal, pregnancy, and neonatal characteristics were collected from obstetric and neonatal records using a standardized questionnaire. Information included maternal

age at delivery, maternal country of birth, parity, multiple birth, premature rupture of membranes, pre-eclampsia/eclampsia/haemolysis, elevated liver enzymes, and low platelets, child sex, birthweight, congenital anomalies, and gestational age. Gestational age was defined as the best estimate determined by the obstetrical team on the basis of information for last menstrual period and antenatal ultrasounds. Small for gestational age was defined as a birthweight less than the 10th centile of European references developed for the cohort.¹⁹ Bronchopulmonary dysplasia was defined as oxygen dependency at 36 weeks postmenstrual age. Severe neonatal morbidity was defined as a composite measure of cystic periventricular leukomalacia, intraventricular haemorrhage grades III and IV, severe necrotizing enterocolitis requiring surgery or peritoneal drainage, or retinopathy of prematurity at least stage 3.

Five-year follow-up

The 5-year follow-up protocol included a neurodevelopmental assessment and a parental questionnaire.

Neurodevelopmental assessments

The Movement Assessment Battery for Children, Second Edition (MABC-2) was administered by trained psychologists or physiotherapists. Assessments were performed by staff in local routine follow-up programmes where available (Belgium, the Netherlands, Sweden) or by the SHIPS research team (Denmark, Estonia, France, Germany, Italy, Poland, Portugal, UK). Although it was not possible to assess interrater reliability across countries, common data collection guidelines and a core data collection form were developed to standardize procedures and to ensure consistent reporting of the assessment results. Training sessions were held locally and an online discussion forum was set up to discuss possible problems emerging during the data collection. The MABC-2²⁰ was used to assess motor development with the original UK norms. Scores greater than the 15th centile indicate no movement difficulties; those greater than the 5th and up to the 15th centiles indicate that the child is at risk of movement difficulties; and scores no greater than the 5th centile denote significant movement difficulties (SMD).²⁰ Eight Belgian children were assessed with the MABC, First Edition,²¹ but the converted centile scores allow the same classification of movement difficulties.

A group composed of neurodevelopmental specialists and an epidemiologist (RC, UA, SJ, and JZ) examined children with missing MABC-2 scores on a case-by-case basis. Where the MABC-2 test could not be completed owing to a severe motor impairment described by the clinical team, a composite score of 1 (i.e. centile 0.1) was assigned ($n = 7$). When a subtest was missing and the child had no other neurosensory or developmental problem that could explain the

missing value, the average of the other subtests was assigned ($n = 11$); otherwise, data were not imputed.

The Wechsler Preschool and Primary Scale of Intelligence Revised, Third Edition, or Fourth Edition^{22,23} was administered to assess full-scale IQ. Scores were calculated using local norms; full-scale IQ scores of at least 85 (> -1 SD) indicate cognition in or above the average range; scores between 70 and 84 (< -1 SD; -2 SD) mild impairment; scores between 55 and 69 (< -2 SD; -3 SD) moderate impairment; and scores no more than 54 (< -3 SD) severe impairment.

Parent-report questionnaires

Data on the children's health, including CP diagnosis, health care use, and parental sociodemographic status, were collected using a parental questionnaire (completed by mothers, fathers, or other caregivers). We used information on mothers' educational level, coded using the International Standard Classification of Education (ISCED)²⁴ into low (ISCED 0–2), intermediate (ISCED 3–5), and high (ISCED 6–8), parental cohabitation status, and household employment status.

Participants indicated the number of visits over the previous year to specific health care providers from a pre-established, pre-tested list adapted to each country.¹⁵ Receiving MRHC was defined as having at least one visit to any of the following: (1) physiotherapist, motor development or psychomotor therapist, or kinesiologist; (2) occupational therapist, or (3) early intervention specialist. Receiving specialized health care was defined as having at least one visit to any of the following: (1) neurologist/developmental paediatrician; (2) psychologist/neuropsychologist or psychiatrist/neuropsychiatrist; (3) speech/language therapist; (4) ear specialist/ear, nose, and throat specialist/hearing test; (5) eye specialist, ophthalmologist, optometrist, or orthoptist; (6) respiratory or allergy specialist; or (7) dietitian or nutritionist. Receiving general health care was defined as having at least one visit in the previous year to any of the following: (1) paediatrician; (2) family doctor/general practitioner; (3) hospital accident and emergency department/hospitalization overnight; or (4) school nurse/nurse/health visitor.

Parents also completed the Strengths and Difficulties Questionnaire²⁵ which is a well-validated and widely used measure of children's behaviour, inattention/hyperactivity, and social and emotional problems over the previous 6 months that provides a total score and five subscales. The scores were categorized as 'normal', 'borderline', or 'abnormal'.²⁶

Statistical analysis

We first described the sociodemographic and clinical characteristics of participants and non-participants. Since there were differences in the follow-up rates by country,¹⁸ these comparisons were adjusted for country using logistic

regression. Then, we reported the median number of visits to health care services, and, using χ^2 tests, we compared the health care services received by children in four groups: no movement difficulties; at risk of movement difficulties; SMD; CP. We compared health care service use by country; however, for our primary analysis we focused on a subset of countries with larger samples (France [$n = 160$], Italy [$n = 137$], Portugal [$n = 94$], and the UK [$n = 102$]). We then investigated factors related to MRHC service use among the combined group of children without CP at risk of movement difficulties or with SMD. Logistic regressions adjusting only for country and adjusting for country and level of motor development (MABC-2 total score) were performed to obtain the odds ratio (OR) and 95% confidence interval (CI) of receiving MRHC among children at risk of movement difficulties or with SMD according to the family socioeconomic characteristics and the child's perinatal and socioemotional characteristics. We performed sensitivity analyses by re-running models with inverse probability weighting to take into account loss to follow-up,^{27,28} as described previously in this cohort.²⁹⁻³¹ All analyses used SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The mean gestational age at birth was 26 weeks 4 days (SD 8 days), the mean birthweight was 876.8g (SD 188.6), and 412 children were male (51.1%) (Table 1). Most children were singleton (71.4%) and about one-quarter were small for gestational age (24.5%) or had severe neonatal morbidity (24.5%). Children who survived to discharge from neonatal care but who were: not followed up at 5 years, had mothers who were younger, non-European born, or multiparous were compared with those followed up (Table S1). There were also fewer pregnancies complicated by pre-eclampsia/eclampsia/haemolysis, elevated liver enzymes, and low platelet count, and fewer infants who were small for gestational age among children not followed up compared with those who were. Children without MABC-2 scores or missing health care data had lower gestational age and birthweight, and their mothers were more likely to be younger, non-European born, and have lower educational level than children in the analysis (Table S2). MABC-2 assessments were performed at an average age of 5 years 7 months (SD 4 months; 4 years 7 months–7 years 1 month). Of the 807 participants included in the analysis (Table 1), 170 (21.1%) were at risk of movement difficulties, 201 (24.9%) had SMD, and 92 (11.4%) had CP.

Most children with CP received MRHC (89.1%) in addition to other specialized health care (91.3%) and general health care (95.7%) (Table 2). These proportions were substantially higher than for children without CP but with SMD or at risk of movement difficulties, especially for MRHC (MRHC, 42.8%/25.9%; other specialized health care, 85.6%/71.2%; and general health care, 89.6%/91.2%). For children without CP and at risk of movement difficulties or with SMD, the

main MRHC providers were physiotherapists, motor development/psychomotor therapists, or kinesiologists (23.5%), followed by early intervention services (12.4%) and occupational therapists (10.5%).

In countries with sample sizes above 90 children, the proportion of children at risk of movement difficulties or with SMD receiving MRHC varied from 4.5%/23.3% in the UK to 33.3%/66.7% in France (Figure 1). Variation in the provision of MRHC for children with CP was lower. Similar patterns were observed for countries with sample sizes below 90 (Figure S2).

Receiving MRHC (Table 3) was associated with unemployment in the household (OR 2.59; 95% CI 1.41–4.76), severe neonatal morbidity (OR 2.26; 95% CI 1.32–3.86), receiving other specialized health care (OR 2.76; 95% CI 1.09–7.00), or general health care (2.82; 95% CI 1.42–5.60). Not receiving MRHC was associated with non-European-born mothers (0.28; 95% CI 0.13–0.63). Children with emotional problems, peer relationship problems, conduct problems, or inattention/hyperactivity or abnormal total scores on the Strengths and Difficulties Questionnaire were more likely to receive MRHC (Table 4). Sensitivity analyses with inverse probability weighting yielded similar results (Tables S3 and S4).

DISCUSSION

This study found high use of MRHC among children born EPT with CP (89.0%), but lower use among children without CP with SMD (42.8%) or at risk of movement difficulties (25.9%). Additionally, there was higher variation in MRHC use between countries for children without CP but at risk of movement difficulties or with SMD, compared with children with CP. Children who received MRHC were most likely to receive it from physiotherapists, motor development/psychomotor therapists, or kinesiologists, followed by early intervention services. The median number of visits to specialized MRHC providers varied between one and two visits per month during the previous year, depending on the service, indicating care beyond a single visit for assessment of motor function. We found that comorbidity with other behavioural, social, or emotional problems, or receiving other specialized or general health care, were associated with a higher likelihood of receiving MRHC.

The low proportion of children with SMD receiving MRHC compared with children with CP is striking. Several non-exclusive hypotheses may explain these low levels of care. First, the duration of routine follow-up for children born EPT may not be long enough to detect evolving movement difficulties in some children. In our cohort, 90.3% children used routine follow-up services at some point after discharge, but at the age of 5 years only 27.3% were using follow-up services.¹⁶ The proportion of children with SMD receiving MRHC was higher in France and Portugal, which have higher rates of routine follow-up at the age of 5 years (31.2% and 58.4%), compared with Italy and the UK (12.3%

TABLE 1 Characteristics of the sample of all children born extremely preterm included in the study overall and by motor status

	Total (n = 807) n (%)	No movement difficulties (n = 344) n (%)	At risk movement difficulties (n = 170) n (%)	SMD (n = 201) n (%)	CP (n = 92) n (%)
Maternal education					
Low ISCED 0–2	138 (17.3)	49 (14.4)	28 (16.7)	45 (22.6)	16 (18.0)
Intermediate ISCED 3–5	341 (42.8)	142 (41.8)	70 (41.7)	88 (44.2)	41 (46.1)
High ISCED 6–8	317 (39.8)	149 (43.8)	70 (41.7)	66 (33.2)	32 (36.0)
Missing	11 (1.4)	4 (1.2)	2 (1.2)	3 (1.5)	3 (3.3)
Household unemployment					
At least one parent unemployed	100 (12.6)	25 (7.3)	31 (18.5)	28 (14.1)	16 (18.4)
Other situations ^a	695 (87.4)	317 (92.7)	137 (81.5)	170 (85.9)	71 (81.6)
Missing	12 (1.5)	2 (0.6)	2 (1.2)	3 (1.5)	5 (5.4)
Parental cohabiting status					
Single parent or other situation	138 (17.2)	58 (16.9)	31 (18.3)	33 (16.6)	16 (17.4)
Married/couple/cohabiting	666 (82.8)	286 (83.1)	138 (81.7)	166 (83.4)	76 (82.6)
Missing	3 (0.4)	0 (0.0)	1 (0.6)	2 (1.0)	0 (0.0)
Maternal age at childbirth (years)					
≤24	87 (10.8)	26 (7.6)	20 (11.9)	28 (13.9)	13 (14.4)
25–34	471 (58.7)	198 (57.6)	111 (66.1)	109 (54.2)	53 (58.9)
≥35	245 (30.5)	120 (34.9)	37 (22.0)	64 (31.8)	24 (26.7)
Missing	4 (0.5)	0 (0.0)	2 (1.2)	0 (0.0)	2 (2.2)
Maternal country of birth					
Native	637 (79.2)	270 (78.9)	142 (84.0)	152 (75.6)	73 (79.3)
Born in another European country	53 (6.6)	19 (5.6)	12 (7.1)	17 (8.5)	5 (5.4)
Born in a non-European country	114 (14.2)	53 (15.5)	15 (8.9)	32 (15.9)	14 (15.2)
Missing	3 (0.4)	2 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)
Parity					
Nulliparous	483 (60.7)	197 (58.3)	116 (69.0)	125 (62.5)	45 (50.0)
Multiparous	313 (39.3)	141 (41.7)	52 (31.0)	75 (37.5)	45 (50.0)
Missing	11 (1.4)	6 (1.7)	2 (1.2)	1 (0.5)	2 (2.2)
Multiple birth					
Singleton	576 (71.4)	225 (65.4)	126 (74.1)	156 (77.6)	69 (75.0)
Multiple	231 (28.6)	119 (34.6)	44 (25.9)	45 (22.4)	23 (25.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PROM					
Yes	199 (24.9)	82 (24.1)	43 (25.6)	52 (26.1)	22 (24.2)
Missing	9 (1.1)	4 (1.2)	2 (1.2)	2 (1.0)	1 (1.1)
Eclampsia/pre-eclampsia/HELLP					
Yes	90 (11.3)	38 (11.1)	19 (11.4)	25 (12.5)	8 (8.8)
Missing	9 (1.1)	3 (0.9)	4 (2.4)	1 (0.5)	1 (1.1)
Sex					
Male	412 (51.1)	137 (39.8)	90 (52.9)	124 (61.7)	61 (66.3)
Female	395 (48.9)	207 (60.2)	80 (47.1)	77 (38.3)	31 (33.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gestational age (completed weeks)					
≤24	82 (10.2)	22 (6.4)	19 (11.2)	29 (14.4)	12 (13.0)
25	153 (19.0)	55 (16.0)	25 (14.7)	45 (22.4)	28 (30.4)
26	239 (29.6)	111 (32.3)	48 (28.2)	59 (29.4)	21 (22.8)
27	333 (41.3)	156 (45.3)	78 (45.9)	68 (33.8)	31 (33.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mean (SD)	27 (1)	2.7 (1)	27 (1)	26 (1)	26 (1)
Birthweight (g)					
Mean (SD)	876.8 (188.6)	902.9 (177.1)	870.4 (203.1)	844.8 (193.8)	860.9 (179.6)

(Continues)

TABLE 1 (Continued)

	Total (n = 807) n (%)	No movement difficulties (n = 344) n (%)	At risk movement difficulties (n = 170) n (%)	SMD (n = 201) n (%)	CP (n = 92) n (%)
SGA (EURO-Peristat)					
<10	198 (24.5)	74 (21.5)	48 (28.2)	58 (28.8)	18 (19.6)
≥10	609 (75.5)	270 (78.5)	122 (71.8)	143 (71.2)	74 (80.4)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital anomalies					
Yes	67 (8.3)	18 (5.2)	10 (5.9)	26 (12.9)	13 (14.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
BPD					
Yes	253 (32.2)	65 (19.6)	58 (34.7)	89 (45.2)	41 (46.1)
Missing	22 (2.7)	12 (3.5)	3 (1.8)	4 (2.0)	3 (3.3)
Severe neonatal morbidity ^b					
Yes	194 (24.5)	45 (13.3)	36 (21.6)	58 (29.4)	55 (61.1)
Missing	15 (1.9)	6 (1.7)	3 (1.8)	4 (2.0)	2 (2.2)
MABC-2 scores ^c					
Mean (SD)	7.1 (3.5)	10.3 (2.0)	6.6 (0.5)	3.6 (1.5)	2.7 (2.6)
Cognitive status ^d					
No impairment	548 (70.6)	300 (88.0)	125 (73.5)	95 (47.7)	28 (42.4)
Mild impairment	158 (20.4)	37 (10.9)	42 (24.7)	64 (32.2)	15 (22.7)
Moderate impairment	57 (7.3)	4 (1.2)	3 (1.8)	40 (20.1)	10 (15.2)
Severe impairment	13 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	13 (19.7)
Missing	31 (3.8)	3 (0.9)	0 (0.0)	2 (1.0)	26 (28.3)
SDQ total score ^e					
Normal	566 (71.1)	276 (80.7)	122 (72.6)	127 (63.8)	41 (47.1)
Borderline	101 (12.7)	32 (9.4)	16 (9.5)	34 (17.1)	19 (21.8)
Abnormal	129 (16.2)	34 (9.9)	30 (17.9)	38 (19.1)	27 (31.0)
Missing	11 (1.4)	2 (0.6)	2 (1.2)	2 (1.0)	5 (5.4)
Country (regions)					
Belgium (Flanders)	47 (5.8)	14 (4.1)	17 (10.0)	8 (4.0)	8 (8.7)
Denmark (eastern region)	42 (5.2)	23 (6.7)	10 (5.9)	7 (3.5)	2 (2.2)
Estonia (entire country)	33 (4.1)	18 (5.2)	3 (1.8)	10 (5.0)	2 (2.2)
France (Burgundy, Ile-de-France, northern region)	160 (19.8)	99 (28.8)	24 (14.1)	15 (7.5)	22 (23.9)
Germany (Hesse, Saarland)	59 (7.3)	28 (8.1)	10 (5.9)	13 (6.5)	8 (8.7)
Italy (Emilia-Romagna, Lazio, Marche)	137 (17.0)	50 (14.5)	29 (17.1)	43 (21.4)	15 (16.3)
The Netherlands (central eastern region)	63 (7.8)	33 (9.6)	21 (12.4)	7 (3.5)	2 (2.2)
Poland (Wielkopolska)	41 (5.1)	4 (1.2)	4 (2.4)	23 (11.4)	10 (10.9)
Portugal (Lisbon, northern region)	94 (11.6)	35 (10.2)	27 (15.9)	26 (12.9)	6 (6.5)
UK (East Midlands, northern, Yorkshire, the Humber)	102 (12.6)	26 (7.6)	22 (12.9)	43 (21.4)	11 (12.0)
Sweden (greater Stockholm)	29 (3.6)	14 (4.1)	3 (1.8)	6 (3.0)	6 (6.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: BPD, bronchopulmonary dysplasia was defined as oxygen dependency at 36 weeks postmenstrual age; PROM, premature rupture of membranes; SGA, small for gestational age was defined as a birthweight less than the 10th centile of European references;¹⁹ ISCED, International Standard Classification of Education; SMD, significant movement difficulties; CP, cerebral palsy; HELLP, hemolysis, elevated liver enzymes, and low platelets count.

^aOther situations included student, parental leave, home parent, and other.

^bDefined as a composite measure of cystic periventricular leukomalacia, intraventricular haemorrhage grades III and IV, necrotizing enterocolitis that required surgery or peritoneal drainage, or retinopathy of prematurity ≥ stage 3.

^cMovement Assessment Battery for Children, Second Edition (MABC-2): for the group of children with CP, scores are available for 71 children, owing to some of these children's inability to perform the assessment.

^dSevere impairment was considered if IQ < 55; moderate impairment was considered if IQ was between 55 and 69; mild impairment was considered if IQ was between 70 and 84; no impairment was considered if IQ ≥ 85.

^eStrengths and Difficulties Questionnaire total score derived from emotional symptoms, conduct problems, hyperactivity/inattention, and peer relationship problems scores.

TABLE 2 Health care use among children born extremely preterm according to movement difficulties and cerebral palsy

	Movement difficulties				
	Number (<i>n</i> = 344) <i>n</i> (%)	Movement difficulties (<i>n</i> = 170) <i>n</i> (%)	SMD (<i>n</i> = 201) <i>n</i> (%)	CP (<i>n</i> = 92) <i>n</i> (%)	Total (<i>n</i> = 807) <i>n</i> (%)
Physiotherapist/motor development or psychomotor therapist/kinesiologist ^a	33 (9.6)	29 (17.1)	58 (28.9)	75 (81.5)	195 (24.2)
Number of visits, ^b median (Q1–Q3)	2.0 (1.0–15.0)	24.0 (1.3–49.0)	14.0 (3.0–52.0)	60.0 (26.0–130.0)	25.0 (3.0–60.0)
Occupational therapist ^a	12 (3.5)	9 (5.3)	30 (14.9)	36 (39.1)	87 (10.8)
Number of visits, ^b median (Q1–Q3)	1.0 (1.0–19.0)	27.0 (2.0–40.0)	16.0 (2.0–46)	35.0 (9.3–59.0)	22.0 (2.0–48.0)
Early intervention ^c	3 (0.9)	13 (7.6)	33 (16.4)	20 (21.7)	69 (8.6)
Number of visits, ^b median (Q1–Q3)	2.0 (2.0–2.0)	8.0 (2.5–33.5)	12.0 (2.0–44.0)	11.0 (5.3–50.0)	10.0 (2.0–40.0)
MRHC ^d	42 (12.2)	44 (25.9)	86 (42.8)	82 (89.1)	254 (31.5)
Number of visits, ^b median (Q1–Q3)	2.0 (1.0–15.5)	24.0 (3.0–45.0)	18.0 (3.0–52.0)	70.0 (31.5–150.0)	26.0 (3.0–60.0)
Other specialized health care ^e	232 (67.4)	121 (71.2)	172 (85.6)	84 (91.3)	609 (75.5)
Number of visits, ^b median (Q1–Q3)	3.0 (1.0–6.8)	3.0 (2.0–11.5)	6.0 (2.0–28.0)	23.0 (5.3–72.8)	4.0 (2.0–18.0)
General health care ^f	314 (91.3)	155 (91.2)	180 (89.6)	88 (95.7)	737 (91.3)
Number of visits, ^b median (Q1–Q3)	3.0 (2.0–6.0)	4.0 (2.0–7.0)	4.0 (2.0–8.0)	7.0 (2.0–18.8)	4.0 (2.0–7.5)
Health care use					
No health care at all	102 (29.7)	34 (20.0)	34 (16.9)	5 (5.4)	175 (21.7)
Only MRHC	1 (0.3)	1 (0.6)	0 (0.0)	1 (1.1)	3 (0.4)
Only other than MRHC	200 (58.1)	92 (54.1)	81 (40.3)	5 (5.4)	378 (46.8)
MRHC and other health care	41 (11.9)	43 (25.3)	86 (42.8)	81 (88.0)	251 (31.1)

Note: Bold type indicates statistically significant results.

Abbreviations: MRHC, motor-related health care; SMD, significant movement difficulties; CP, cerebral palsy.

^aAt least one visit to any of these specialists over the previous year.

^bNumber of visits calculated for participants that reported at least one visit over the previous year.

^cAt least one visit over the previous year.

^dDefined as having at least one visit to a motor-related health specialist over the previous year: (1) physiotherapist, motor development or psychomotor therapist, or kinesiologist; (2) occupational therapist; or (3) early intervention specialist.

^eDefined as having at least one visit in the previous year to a (1) neurologist/developmental paediatrician; (2) psychologist/neuropsychologist or psychiatrist/neuropsychiatrist; (3) speech/language therapist; (4) ear specialist/ear, nose, and throat specialist/hearing test; (5) eye specialist, ophthalmologist, optometrist, or orthoptist; (6) respiratory specialist or allergologist; or (7) dietitian or nutritionist.

^fDefined as having at least one visit in the previous year to (1) paediatrician; (2) family doctor/general practitioner; (3) hospital accident and emergency department/hospitalization overnight; or (4) school nurse/nurse/health visitor.

and 17.0%).¹⁶ Longer systematic follow-up beyond 2 years of age may be needed to identify children with movement difficulties, since about one-third of children born preterm with CP are only diagnosed after 2 years 6 months of age³² and because motor skills may decline until at least the age of 5 years in children born very preterm, especially for those who had higher scores on tests of motor performance at the age of 2 years.³³

A second hypothesis is that movement difficulties may not be assessed as part of routine clinical follow-up protocols. The European Foundation for the Care of Newborn Infants Standards of Care for children born very preterm recommends conducting several assessments of motor development in the first 2 years and again at transition to school.¹¹ We currently lack information about the extent to which the follow-up protocols follow these recommendations, including whether motor function is part of those protocols, at what ages it is assessed, how it is assessed, and whether specific risk-groups are targeted. In some follow-up

programmes, movement difficulties may not be recognized as a developmental area in need of assessment, meaning it would only be assessed within the scope of in-depth neuro-developmental assessments when there is suspicion of other developmental problems.

Another hypothesis might be that parents of children born EPT underestimate children's motor problems.³⁴ They may not feel that these difficulties affect the child's daily life, and therefore they do not recognize them as problematic, especially if the child has no other behavioural or emotional problems. Similarly, movement difficulties with subtle or no ostensible impact on the child's daily activities may be underestimated or undiagnosed by health care providers;³⁵ or providers may be reluctant to refer the child for care, particularly in contexts where there is insufficient supply of services in both the private and the public sectors even for children born preterm with more complex special needs.^{36–38} This would be of concern because some health care interventions have yielded benefits for children with

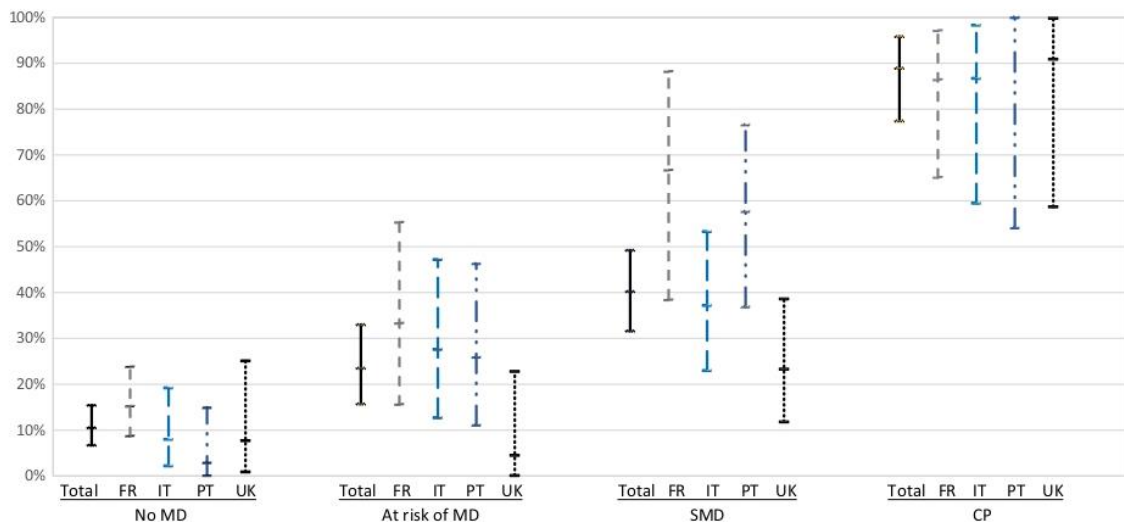


FIGURE 1 Percentage of children born extremely preterm who received motor-related health care (MRHC) with 95% confidence intervals according to motor status in France, Italy, Portugal, and the UK. MRHC is defined as having at least one visit to any MRHC specialist over the last year: (1) physiotherapist, motor development or psychomotor therapist, or kinesiologist; (2) occupational therapist; or (3) early intervention specialist. Abbreviations: MD, movement difficulties; SMD, significant movement difficulties; CP, cerebral palsy; FR, France; IT, Italy; PT, Portugal; UK, United Kingdom

developmental coordination disorder.^{12,39–40} Another possibility is that health care providers believe that movement difficulties with subtle impacts on daily activities will be overcome with preschool activities that promote fine and gross motor skills.

Large differences in the use of MRHC for children with SMD were observed by country which may be explained by variability in routine follow-up protocols and intervention approaches, as described above, or potentially by service availability.¹⁷ Heterogeneity is known to exist between countries in routine follow-up policies and programmes,¹⁶ but we did not collect information on the specific follow-up protocols used for motor function assessment for the children in our sample. Our data come from selected regions in each country – except for Estonia where the entire country is represented – and therefore results may not be representative of the situation in the whole country given regional differences in the organization of follow-up services and health care provision. Further research comparing follow-up for these children in more detail in regions and countries with different levels of MRHC use could help refine explanatory hypotheses.

These geographical differences illustrate a lack of consensus on optimal care for children with movement difficulties, which is reflected in the absence of international guidelines for the follow-up of children born EPT without a formal diagnosis of impairment⁴¹ until very recently.¹¹ Indeed, health care providers are more likely to work with children with a diagnosed condition.⁴² This hypothesis is consistent with the much lower variation between countries in MRHC provided to children with a formal diagnosis of CP, for which there are established guidelines for health care provision.^{43–45} This suggests that implementation of the recently published

European standards for developmental follow-up care¹¹ and the international clinical practice on recommendations for intervention in children with developmental coordination disorder⁴⁶ may improve recognition and treatment of health conditions.⁴⁷

Children born EPT with perinatal risk factors for health and developmental problems had increased use of specialized health care, including MRHC, as also found in our sample at 2 years.¹⁵ In contrast, children of non-European-born mothers were less likely to receive MRHC, which is consistent with data showing these children are less likely to use routine follow-up services¹⁶ and with reports of barriers to accessing appropriate health care faced by migrant parents with newborn infants or young children.⁴⁸ Having at least one parent unemployed was associated with greater use of MRHC, but causality is hard to assess because parents may drop out of the workforce when children require a lot of care.⁴⁹ Reassuringly, other social indicators such as maternal age, educational level, or family situation were not associated with the likelihood of health care use. Nevertheless, since non-participation in our study was more common among younger, non-native, and less educated mothers, this population may be underrepresented.

The strengths of this study are data from a population-based cohort with a large sample of children born EPT followed until 5 years of age in 11 countries in Europe. Another strength is standardized and harmonized data collection, including data collected at baseline from medical records, parental report questionnaires, and motor assessments using the same instrument across countries. Limitations include parent-reported information on health care service use, which may be subject to recall bias. Furthermore, we did not have information on the purpose of the health care received

TABLE 3 Social and clinical characteristics associated with receiving motor-related health care (MRHC) among children without cerebral palsy at risk of movement difficulties or with significant movement difficulties

	MRHC ^a			Model 1 ^b		Model 2 ^c	
	No, n (%)	Yes, n (%)	Total, n	OR	95% CI	OR	95% CI
Maternal age at childbirth (years)							
<25	31 (64.6)	17 (35.4)	48	0.94	0.44–2.03	0.94	0.42–2.08
25–34	146 (66.4)	74 (33.6)	220	0.92	0.54–1.55	1.04	0.60–1.80
≥35	63 (62.4)	38 (37.6)	101	Ref.		Ref.	
Maternal education							
Low education ISCED 0–2	45 (61.6)	28 (38.4)	73	1.09	0.57–2.09	0.82	0.41–1.63
Intermediate education ISCED 3–5	98 (62.0)	60 (38.0)	158	1.70	1.00–2.88	1.52	0.88–2.64
High education ISCED 6–8	96 (70.6)	40 (29.4)	136	Ref.		Ref.	
Maternal country of birth							
Native	187 (63.6)	107 (36.4)	294	Ref.		Ref.	
Born in another European country	17 (58.6)	12 (41.4)	29	1.19	0.52–2.69	1.09	0.46–2.56
Born in a non-European country	36 (76.6)	11 (23.4)	47	0.42	0.20–0.88	0.29	0.13–0.64
Household unemployment							
At least one parent unemployed	29 (49.2)	30 (50.8)	59	2.26	1.26–4.06	2.48	1.34–4.58
Other situations ^d	211 (68.7)	96 (31.3)	307	Ref.		Ref.	
Parental cohabitation status							
Single parent or other situation	39 (60.9)	25 (39.1)	64	Ref.		Ref.	
Married/couple/cohabiting	201 (66.1)	103 (33.9)	304	0.84	0.47–1.51	0.79	0.43–1.45
Parity							
Nulliparous	152 (63.1)	89 (36.9)	241	Ref.		Ref.	
Multiparous	88 (69.3)	39 (30.7)	127	0.76	0.47–1.23	0.72	0.43–1.20
Multiple gestation							
Singleton	182 (64.5)	100 (35.5)	282	Ref.		Ref.	
Multiple	59 (66.3)	30 (33.7)	89	0.94	0.55–1.59	1.00	0.58–1.73
Premature rupture of membranes							
Yes	57 (60.0)	38 (40.0)	95	1.19	0.72–1.97	1.20	0.71–2.04
No	180 (66.2)	92 (33.8)	272	Ref.		Ref.	
Pre-eclampsia/eclampsia/HELLP							
Yes	25 (56.8)	19 (43.2)	44	1.25	0.64–2.44	1.17	0.59–2.36
No	211 (65.5)	111 (34.5)	322	Ref.		Ref.	
Sex							
Male	128 (59.8)	86 (40.2)	214	1.59	1.00–2.53	1.41	0.87–2.28
Female	113 (72.0)	44 (28.0)	157	Ref.		Ref.	
Gestational age (completed weeks)							
≤24	30 (62.5)	18 (37.5)	48	1.38	0.67–2.87	1.18	0.55–2.54
25	36 (51.4)	34 (48.6)	70	2.21	1.19–4.11	1.77	0.93–3.36
26	76 (71.0)	31 (29.0)	107	0.82	0.47–1.44	0.72	0.40–1.30
27	99 (67.8)	47 (32.2)	146	Ref.		Ref.	
Mean (SD)	27 (1)	26 (1)	371				

(Continues)

(Continues)

TABLE 3 (Continued)

	MRHC ^a			Model 1 ^b		Model 2 ^c	
	No, <i>n</i> (%)	Yes, <i>n</i> (%)	Total, <i>n</i>	OR	95% CI	OR	95% CI
SGA ^e (EURO-Peristat)							
<10	62 (58.5)	44 (41.5)	106	0.73	0.45–1.18	0.74	0.44–1.22
≥10	179 (67.5)	86 (32.5)	265	Ref.		Ref.	
Congenital anomalies							
No	223 (66.6)	112 (33.4)	335	Ref.		Ref.	
Yes	18 (50.0)	18 (50.0)	36	2.08	0.96–4.50	1.52	0.67–3.46
BPD ^f							
No	146 (67.3)	71 (32.7)	217	Ref.		Ref.	
Yes	91 (61.9)	56 (38.1)	147	1.66	1.02–2.68	1.43	0.86–2.37
Severe neonatal morbidity ^g							
No	190 (70.4)	80 (29.6)	270	Ref.		Ref.	
Yes	48 (51.1)	46 (48.9)	94	2.59	1.55–4.34	2.29	1.34–3.91
Use of specialized health care ^h							
No	65 (83.3)	13 (16.7)	78	Ref.		Ref.	
Yes	176 (60.1)	117 (39.9)	293	3.34	1.71–6.53	2.82	1.42–5.60
Use of general health care ⁱ							
No	29 (80.6)	7 (19.4)	36	Ref.		Ref.	
Yes	212 (63.3)	123 (36.7)	335	2.25	0.92–5.47	2.76	1.09–7.00

Note: Bold type indicates statistically significant results.

Abbreviations: OR, odds ratio; CI, confidence interval; ISCED, International Standard Classification of Education; HELLP, hemolysis, elevated liver enzymes, and low platelets count.

^aMRHC was defined as having at least one visit to a motor-related health specialist over the previous year: (1) physiotherapist, motor development or psychomotor therapist, or kinesiologist; (2) occupational therapist; or (3) early intervention specialist.

^bModel 1 was adjusted for country.

^cModel 2 was adjusted for country and total score on the Movement Assessment Battery for Children, Second Edition.

^dOther situations included student, parental leave, home parent, and other.

^eSGA, small for gestational age was defined as a birthweight less than the 10th centile of European references.¹⁹

^fBPD, bronchopulmonary dysplasia was defined as oxygen dependency at 36 weeks postmenstrual age.

^gSevere neonatal morbidity was defined as a composite measure of cystic periventricular leukomalacia, intraventricular haemorrhage grades III and IV, necrotizing enterocolitis that required surgery or peritoneal drainage, or retinopathy of prematurity ≥ stage 3.

^hUse of specialized health care was defined as having at least one visit in the previous year to any of the following: (1) neurologist/developmental paediatrician; (2) psychologist/neuropsychologist or psychiatrist/neuropsychiatrist; (3) speech/language therapist; (4) ear specialist/ear, nose, and throat specialist/hearing test; (5) eye specialist, ophthalmologist, optometrist, or orthoptist; (6) respiratory specialist or allergologist; or (7) dietitian or nutritionist.

ⁱUse of general health care was defined as having at least one visit in the previous year to any of the following: (1) paediatrician; (2) family doctor/general practitioner; (3) hospital accident and emergency department/hospitalization overnight; or (4) school nurse/nurse/health visitor.

and whether they were for assessment or intervention. We also relied on parental reports of CP diagnosis. However, given the high use of health care services in this sample, in general it is likely that most children with CP would have received a diagnosis by the age of 5 years. Additionally, we have considered early intervention in the category of MRHC since, in the participating countries, early intervention is delivered by multidisciplinary professionals who include MRHC professionals. Still, some children undergoing early intervention may not be receiving MRHC which may have led to an overestimation of MRHC use.

As the study cohort was composed of children born EPT without a comparison group, assessors were not blinded to the very preterm status of children participating in the study which might have led to some bias. However, the MABC-2 is

a well-established research tool with objective subtests and clear administration and interpretation instructions.^{20,21} Finally, study attrition was a challenge in this cohort, including differences by region as discussed previously,¹⁸ and by social factors, with lower social status among families lost to follow-up which may be associated with lower access to health care, meaning our results may have overestimated health care use. Because we had full data on the cohort at inclusion, we were able to conduct sensitivity analyses using inverse probability weighting to adjust for loss to follow-up and found similar results. However, children born EPT with other impairments and risk factors were less likely to be able to participate in the MABC-2 assessment and had missing data which may have underestimated the prevalence of movement difficulties and health care use.

TABLE 4 Cognitive, behavioural, and socioemotional problems associated with receiving motor-related health care (MRHC) among children born extremely preterm at risk of movement difficulties or with significant movement difficulties

	MRHC ^a			Model 1 ^b		Model 2 ^c	
	No, n (%)	Yes, n (%)	Total, n (%)	OR	95% CI	OR	95% CI
Cognitive status ^d							
No impairment	154 (69.7)	67 (30.3)	221	Ref.		Ref.	
Mild impairment	67 (63.2)	39 (36.8)	106	1.42	0.84–2.40	1.15	0.66–1.98
Moderate impairment	18 (41.9)	25 (58.1)	43	3.62	1.73–7.56	1.76	0.78–3.97
Internalizing problems							
Emotional symptoms							
Normal	181 (65.3)	96 (34.7)	277	Ref.		Ref.	
Borderline	28 (70.0)	12 (30.0)	40	0.88	0.42–1.87	0.79	0.36–1.73
Abnormal	28 (54.9)	23 (45.1)	51	1.63	0.86–3.06	1.77	0.92–3.42
Peer relationship problems							
Normal	181 (69.3)	80 (30.7)	261	Ref.		Ref.	
Borderline	23 (59.0)	16 (41.0)	39	1.57	0.76–3.24	1.45	0.68–3.09
Abnormal	33 (48.5)	35 (51.5)	68	2.31	1.31–4.07	1.93	1.07–3.49
Externalizing problems							
Conduct problems							
Normal	152 (67.6)	73 (32.4)	225	Ref.		Ref.	
Borderline	39 (52.7)	35 (47.3)	74	1.85	1.05–3.28	2.16	1.19–3.94
Abnormal	47 (67.1)	23 (32.9)	70	0.90	0.49–1.64	0.85	0.45–1.60
Hyperactivity/inattention							
Normal	161 (72.5)	61 (27.5)	222	Ref.		Ref.	
Borderline	25 (50.0)	25 (50.0)	50	3.04	1.57–5.88	2.74	1.38–5.43
Abnormal	52 (53.6)	45 (46.4)	97	2.21	1.30–3.77	1.88	1.08–3.26
Prosocial behaviour							
Normal	214 (66.9)	106 (33.1)	320	Ref.		Ref.	
Borderline	15 (48.4)	16 (51.6)	31	2.10	0.97–4.55	1.83	0.82–4.08
Abnormal	8 (47.1)	9 (52.9)	17	1.95	0.68–5.61	1.96	0.65–5.87
Strengths and Difficulties Questionnaire total score ^e							
Normal	175 (70.0)	75 (30.0)	250	Ref.		Ref.	
Borderline	22 (44.0)	28 (56.0)	50	3.40	1.75–6.62	2.73	1.37–5.47
Abnormal	40 (58.8)	28 (41.2)	68	1.56	0.87–2.80	1.31	0.71–2.41

Note: Bold type indicates statistically significant results.

Abbreviations: OR, odds ratio; CI, confidence interval.

^aMRHC was defined as having at least one visit to any of the following motor-related health specialists over the previous year: (1) physiotherapist, motor development or psychomotor therapist, or kinesiologist; (2) occupational therapist; or (3) early intervention specialist.

^bModel 1 was adjusted for country.

^cModel 2 was adjusted for country and total score on the Movement Assessment Battery for Children, Second Edition.

^dModerate impairment was considered if IQ was between 55 and 69; mild impairment was considered if IQ was between 70 and 84; no impairment was considered if IQ ≥ 85.

^eStrengths and Difficulties Questionnaire total score derived from emotional symptoms, conduct problems, hyperactivity/inattention, and peer relationship problems.

CONCLUSION

SMD among children without CP were frequent, but most of these children were not receiving MRHC. Our results suggest that efforts are needed to increase awareness and treatment of movement difficulties in the EPT population. Standardized clinical guidelines incorporating screening and assessment for detecting motor problems in early childhood may increase recognition of these problems and

early instigation of specialized interventions in this at-risk population.

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DATA AVAILABILITY STATEMENT

Due to the ethical and privacy authorizations for the SHIPS study, supporting data cannot be made openly available. Further information about the data and conditions for access are available from the authors.

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REFERENCES

1. Brown L, Burns YR, Watter P, Gibbons KS, Gray PH. Motor performance, postural stability and behaviour of non-disabled extremely preterm or extremely low birth weight children at four to five years of age. *Early Hum Dev.* 2015;91(5):309–15. <https://doi.org/10.1016/j.earlhumdev.2015.03.003>.
2. Janssen A, Oostendorp R, Akkermans RP, Steiner K, Kollée LAA, Nijhuis-van der Sanden M. High variability of individual longitudinal motor performance over five years in very preterm infants. *Res Dev Disabil.* 2016;59:306–17. <https://doi.org/10.1016/j.ridd.2016.09.017>.
3. Pierrat V, Marchand-Martin L, Marret S, Arnaud C, Benhammou V, Cambonie G, et al. Neurodevelopmental outcomes at age 5 among children born preterm: EPIPAGE-2 cohort study. *BMJ.* 2021;373:n741. <https://doi.org/10.1136/bmj.n741>. Published 2021 Apr 28.
4. Spittle A. Understanding the relationship between behavioural and motor impairments in extremely low birthweight preterm children. *Acta Paediatr.* 2017;106(4):526–27. <https://doi.org/10.1111/apa.13759>.
5. Lingam R, Golding J, Jongmans MJ, Hunt LP, Ellis M, Emond A. The association between developmental coordination disorder and other developmental traits. *Pediatrics.* 2010;126(5):e1109–e1118. <https://doi.org/10.1542/peds.2009-2789>.
6. Lingam R, Jongmans MJ, Ellis M, Hunt LP, Golding J, Emond A. Mental health difficulties in children with developmental coordination disorder. *Pediatrics.* 2012;129(4):e882–e891. <https://doi.org/10.1542/peds.2011-1556>.
7. Schoemaker M, Lingam R, Jongmans M, van Heuvelen M, Emond A. Is severity of motor coordination difficulties related to comorbidity in children at risk for developmental coordination disorder? *Res Dev Disabil.* 2013;34(10):3084–91. <https://doi.org/10.1016/j.ridd.2013.06.028>.
8. Gu Z, Serradj N, Ueno M, Liang M, Li J, Bacceti ML, et al. Skilled movements require non-apoptotic Bax/Bak pathway-mediated corticospinal circuit reorganization. *Neuron.* 2017;94(3):626–41.e4. <https://doi.org/10.1016/j.neuron.2017.04.019>.
9. Chakrabarty S, Martin JH. Postnatal development of a segmental switch enables corticospinal tract transmission to spinal forelimb motor circuits. *J Neurosci.* 2010;30(6):2277–2288. <https://doi.org/10.1523/JNEUROSCI.5286-09.2010>.
10. Chorna O, Cioni G, Guzzetta A. Principles of early intervention. *Handb Clin Neurol.* 2020;174:333–41. <https://doi.org/10.1016/B978-0-444-64148-9.00024-7>.
11. EFCNI, Hadders-Algra M, Vollmer B et al. European Standards of Care for Newborn Health: Motor and neurological follow-up assessment. 2018 [Internet]. <https://newborn-health-standards.org/motor-neurological-assessment/>
12. Smits-engelsman Bcm, Blank R, Van der kaay A-c, Mosterd-van der meijis R, Vlugt-van den brand E, Polatajko Hj, et al. Efficacy of interventions to improve motor performance in children with developmental coordination disorder: a combined systematic review and meta-analysis. *Dev Med Child Neurol.* 2013;55(3):229–37. <https://doi.org/10.1111/dmcn.12008>.
13. Spittle A, Orton J, Anderson PJ, Boyd R, Doyle LW. Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. *Cochrane Database Syst Rev.* 2015; 11: CD005495. Published 2015 Nov 24. doi:<https://doi.org/10.1002/14651858.CD005495.pub4>
14. Spittle AJ, Orton J. Cerebral palsy and developmental coordination disorder in children born preterm. *Semin Fetal Neonatal Med.* 2014;19(2):84–9. <https://doi.org/10.1016/j.siny.2013.11.005>.
15. Seppänen A-V, Bodeau-Livinec F, Boyle EM, Edstedt-Bonamy A-K, Cuttini M, Toome L, et al. Specialist health care services use in a European cohort of infants born very preterm. *Dev Med Child Neurol.* 2019;61(7):832–39. <https://doi.org/10.1111/dmcn.14112>. Epub 2018 Dec 3 PMID: 30508225.
16. Seppänen A-V, Draper ES, Petrou S, Barros H, Andronis L, Kim SW, et al. Follow-up after very preterm birth in Europe [published online ahead of print, 2021 Feb 10]. *Arch Dis Child Fetal Neonatal*

- Ed. 2021;107(1):113–114 fetalneonatal-2020-320823. <https://doi.org/10.1136/archdischild-2020-320823>.
17. Hilderman CG, Harris SR. Early intervention post-hospital discharge for infants born preterm. *Phys Ther.* 2014;94(9):1211–19. <https://doi.org/10.2522/ptj.20130392>.
 18. Zeitlin J, Maier RF, Cuttini M, Aden U, Boerch K, Gadzinowski J, et al. Cohort profile: Effective Perinatal Intensive Care in Europe (EPICE) very preterm birth cohort. *Int J Epidemiol.* 2020;49(2):372–86. <https://doi.org/10.1093/ije/dyz270>.
 19. Zeitlin J, Bonamy A-KE, Piedvache A, Cuttini M, Barros H, Van Reempts P, et al. Variation in term birth weight across European countries affects the prevalence of small for gestational age among very preterm infants. *Acta Paediatr.* 2017;106(9):1447–55. <https://doi.org/10.1111/apa.13899>.
 20. Henderson SE, Sugden DA, Barnett AL. *Movement Assessment Battery for Children*, 2nd edn. Psychological Corporation; 2007.
 21. Henderson SE, Sugden DA. *Movement Assessment Battery for Children*. Psychological Corporation; 1992.
 22. NCS Pearson I. *Wechsler Preschool and Primary Scale of Intelligence™ - Third Edition (WPPSI™ - III)*. NCS Pearson; 2016a.
 23. NCS Pearson I. *Wechsler Preschool and Primary Scale of Intelligence™ - Fourth Edition (WPPSI™ - IV)*. NCS Pearson; 2016b.
 24. United Nations Educational, Scientific and Cultural Organization (2012). *International Standard Classification of Education. ISCED; 2011*. [Internet]. <http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-isced-2011-en.pdf> (accessed 20th December 2020).
 25. Goodman R. Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry.* 2001;40(11):1337–45. <https://doi.org/10.1097/00004583-200111000-00015>.
 26. EHCAP. *Scoring the Strengths & Difficulties Questionnaire for age 4-17; 2014* [Internet]. <https://www.ehcap.co.uk/content/sites/ehcap/uploads/NewsDocuments/236/SDQEnglishUK4-17scoring-1.PDF> (accessed 3rd February 2021).
 27. Hernán MA, Robins JM. Estimating causal effects from epidemiological data. *J Epidemiol Community Health.* 2006;60(7):578–586. <https://doi.org/10.1136/jech.2004.029496>.
 28. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res.* 2013;22(3):278–295. <https://doi.org/10.1177/0962280210395740>.
 29. Bonnet C, Blondel B, Piedvache A, Wilson E, Bonamy A-KE, Gortner L et al. Low breastfeeding continuation to 6 months for very preterm infants: A European multiregional cohort study. *Matern Child Nutr.* 2019;15(1):e12657. <https://doi.org/10.1111/mcn.12657>.
 30. Seppänen A-V, Sauvegrain P, Draper ES, Toome L, El Rafei R, Petrou S, et al. Parents' ratings of post-discharge healthcare for their children born very preterm and their suggestions for improvement: a European cohort study. *Pediatr Res.* 2021;89(4):1004–1012. <https://doi.org/10.1038/s41390-020-01120-y>.
 31. Piedvache A, van Buuren S, Barros H, Ribeiro AI, Draper E, Zeitlin J, et al. Strategies for assessing the impact of loss to follow-up on estimates of neurodevelopmental impairment in a very preterm cohort at 2 years of age. *BMC Med Res Methodol.* 2021;21(1):118. <https://doi.org/10.1186/s12874-021-01264-3>.
 32. Hafström M, Källén K, Serenius F, Maršál K, Rehn E, Drake H, et al. Cerebral palsy in extremely preterm infants. *Pediatrics.* 2018;141(1):e20171433. <https://doi.org/10.1542/peds.2017-1433>.
 33. Lean RE, Paul RA, Smyser TA, Smyser CD, Rogers CE. Social adversity and cognitive, language, and motor development of very preterm children from 2 to 5 years of age. *J Pediatr.* 2018;203:177–184.e1. <https://doi.org/10.1016/j.jpeds.2018.07.110>.
 34. 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. <https://doi.org/10.1001/jamapediatrics.2018.1394>.
 35. Harris SR, Mickelson ECR, Zwicker JG. Diagnosis and management of developmental coordination disorder. *CMAJ.* 2015;187(9):659–665. <https://doi.org/10.1503/cmaj.140994>.
 36. Brenner M, Kidston C, Hilliard C, Coyne I, Eustace-Cook J, Doyle C, et al. Children's complex care needs: a systematic concept analysis of multidisciplinary language. *Eur J Pediatr.* 2018a;177(11):1641–52.
 37. Brenner M, O'Shea MP, Larkin P, Luzi D, Pecoraro F, Tamburis O, et al. Management and integration of care for children living with complex care needs at the acute-community interface in Europe. *Lancet Child Adolesc Health.* 2018b;2(11):822–31.
 38. Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes. In Behrman RE, Butler AS editors. *Preterm Birth: Causes, Consequences, and Prevention*. National Academies Press (US); 2007.
 39. Biotteau M, Albaret JM, Chaix Y. Developmental coordination disorder. *Handb Clin Neurol.* 2020;174:3–20. <https://doi.org/10.1016/B978-0-444-64148-9.00001-6>.
 40. Novak I, Morgan C. High-risk follow-up: Early intervention and rehabilitation. *Handb Clin Neurol.* 2019;162:483–510. <https://doi.org/10.1016/B978-0-444-64029-1.00023-0>.
 41. Orton JL, Olsen JE, Ong K, Lester R, Spittle AJ. NICU graduates: the role of the allied health team in follow-up. *Pediatr Ann.* 2018;47(4):e165–e171. <https://doi.org/10.3928/19382359-20180325-02>.
 42. Raspa M, Hebbeler K, Bailey DBJ, Scarborough AA. Service provider combinations and the delivery of early intervention services to children and families. *Infants Young Children.* 2010;23(2):132–44.
 43. Agency for Clinical Innovation. *Management of Cerebral Palsy in Children - A Guide for Allied Health Professionals: Guideline*. NSW Ministry of Health; 2018.
 44. Morgan C, Fetters L, Adde L, Badawi N, Bancale A, Boyd RN, et al. Early intervention for children aged 0 to 2 years with or at high risk of cerebral palsy: international clinical practice guideline based on systematic reviews. *JAMA Pediatr.* 2021;175(8):846. doi:<https://doi.org/10.1001/jamapediatrics.2021.0878>
 45. National Institute for Health and Care Excellence. *Cerebral palsy in under 25s: assessment and management*. National Institute for Health and Care Excellence [Internet]; 2017. www.nice.org.uk/guidance/NG62 (accessed 11st February 2021).
 46. Blank R, Barnett AL, Cairney J, Green D, Kirby A, Polatajko H, et al. International clinical practice recommendations on the definition, diagnosis, assessment, intervention, and psychosocial aspects of developmental coordination disorder. *Dev Med Child Neurol.* 2019;61(3):242–85. <https://doi.org/10.1111/dmcn.14132>.
 47. Torjesen I. NICE publishes guideline on diagnosing and managing cerebral palsy in young people. *BMJ.* 2017;356: j462.
 48. Dougherty L, Lloyd J, Harris E, Caffrey P, Harris M. Access to appropriate health care for non-English speaking migrant families with a newborn/young child: a systematic scoping literature review. *BMC Health Serv Res.* 2020;20(1):309. <https://doi.org/10.1186/s12913-020-05157-x>. Published 2020 Apr 15.
 49. Saurel-Cubizolles M-J, Marchand-Martin L, Pierrat V, Arnaud C, Burguet A, Fresson J, et al. Maternal employment and socio-economic status of families raising children born very preterm with motor or cognitive impairments: the EPIPAGE cohort study. *Dev Med Child Neurol.* 2020;62(10):1182–90.

SUPPORTING INFORMATION

The following additional material may be found online.

Table S1: Characteristics associated with loss to follow-up.

Table S2: Participants included in the analysis vs participants in the study follow-up excluded from the main analysis.

Table S3: Social and clinical characteristics associated with receiving motor-related health care among children without CP at risk of movement difficulties or with significant movement difficulties.

Table S4: Cognitive, behavioral, and socioemotional problems associated with receiving motor-related health care among extremely preterm children at risk of movement difficulties or with significant movement difficulties.

Figure S1: Participation flowchart.

Figure S2: Percentage of children born extremely preterm who received motor-related health care with 95% confidence intervals according to motor status overall and by country.

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Chapter 7 – Movement difficulties and health-related quality of life among five-year-old children born extremely preterm

7.1. Preface

As CP and non-CP MD affect about 60% of children born EPT and given that the majority of them, except for children with CP, are not receiving MRHC services, a remaining question is to assess if these developmental motor problems have an impact on their ability to carry out activities of daily life. In the literature, very few studies have assessed the HRQoL of children born EPT and even less its link with developmental difficulties including motor problems. HRQoL which is more and more commonly used in complement to traditional medical measures, has become a key outcome for the child, the parents and healthcare professionals, as well as what the society wants for all children.

We found that compared to EPT children without MD, developmental motor problems were associated with poorer HRQoL, with the lowest level for children with CP, followed by those with significant MD and at risk for MD. These results remained similar after adjustment on family sociodemographic characteristics. Differences were slightly attenuated but persisted after exclusion of children with a moderate to severe NDI and among children not receiving any MRHC services over the past year. These results illustrate the concrete detrimental impact of developmental motor problems on the lives of children and support calls for continued follow-up of children born EPT and greater attention to motor function in follow-up. The quantile regression analysis provided an additional perspective on these associations by showing the heterogeneous association of motor problems with HRQoL. For children with CP, decreases were observed at all quantiles of the outcome, whereas for children with non-CP MD, decreases were non-significant at quantile 90 and more pronounced at the lower HRQoL quantiles. The last point suggests that there may be mitigating or protective factors that preserve HRQoL for some children and raises questions for future studies about protective individual, familial or broader environmental factors.

This work is presented here as a submitted, pre-peer review manuscript. Supplemental material is inserted at the end of the manuscript (*Supplemental material – Chapter 7*). These results were also presented as a podium presentation at the 35th Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research (Chicago, the United States, 2022, June 13-14), at the 9th Congress of the European Academy of Paediatric Societies (Barcelona, Spain, 2022, October 7-11), and at the 15th Association of Schools of Public Health in the European Region Young Researchers Forum (Berlin, Germany, 2022, November 9), and as poster presentation at the Society for Epidemiologic Research (Chicago, the United States, 2022, June 15-17) and at the 15th European Public Health Conference (Berlin, Germany, 2022, November 9-12).

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2 **Movement difficulties and health-related quality of life among five-year-old children born**
3 **extremely preterm in a European multi-country cohort**

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70

71 Abbreviations:

72 CCTIRS, French Advisory Committee on Use of Health Data in Medical Research

73 CI, Confidence interval

74 CLAD, Censored least absolute deviations (model)

75 CNIL, French National Commission for Data Protection and Liberties

76 CP, Cerebral palsy

77 DCD, Developmental coordination disorder

78 EPICE, Effective Perinatal Intensive Care in Europe

79 EPT, Extremely preterm

80 GA, Gestational age

81 HRQOL, Health-related quality of life

82 IPW, Inverse probability weighting

83 IQ, Intelligence quotient

84 MABC, Movement Assessment Battery for Children (1st edition)

85 MABC-2, Movement Assessment Battery for Children (2nd edition)

86 MD, Movement difficulties

87 MRHC, Motor-related health care

88 NDI, Neurodevelopmental impairment

89 PedsQL, Pediatric Quality of Life Inventory™

90 SD, Standard deviation

91 SHIPS, Screening to Improve Health in Very Preterm Infants in Europe

92 VPT, Very preterm

93

94

95 **Contributors' Statement:**
96 Aubert and Zeitlin conceptualized and designed the study, carried out the different analyses,
97 drafted the initial manuscript, and reviewed and revised the manuscript.
98 Costa, Johnson, Ådén, Pierrat and Sentenac supervised the different analyses, and critically
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100 Cuttini, Männamaa, Sarrechia, Lebeer, van Heijst and Maier contributed to the study design,
101 participated in data collection and curation and critically reviewed and revised the manuscript
102 for important intellectual content.
103 All authors approved the final manuscript as submitted and agree to be accountable for all
104 aspects of the work.

105 **Abstract**

106 **Aim**

107 To measure the association between cerebral palsy (CP) and non-CP movement difficulties
108 (MD) and health-related quality of life (HRQoL) among five-year-old children born extremely
109 preterm (EPT, <28 weeks' gestational age).

110

111 **Methods**

112 We included five-year-old children from a multi-country population-based cohort of EPT births
113 in 2011-2012 in 11 European countries (N=1,021). Children without CP were classified using
114 the Movement Assessment Battery for Children-2nd edition as having significant MD ($\leq 5^{\text{th}}$
115 percentile of standardized norms) or being at risk of MD (6^{th} - 15^{th} percentile). Parents reported
116 on a clinical CP diagnosis and HRQoL using the Pediatric Quality of Life InventoryTM.

117

118 **Results**

119 Compared to children without MD, children with CP, significant MD or at risk of MD had lower
120 adjusted HRQoL total scores (Beta [95% confidence intervals]): -26.1 [-31.0,-21.2], -9.1 [-12.0,-
121 6.1] and -5.0 [-7.7,-2.3], respectively. These differences persisted among children without
122 other neurodevelopmental impairments and those not receiving motor-related health care
123 services. Quantile regression analyses showed similar decreases in HRQoL for children with CP
124 at all percentiles, but effects were heterogeneous and more pronounced at lower percentiles
125 for children with non-CP MD.

126

127 **Interpretation**

128 CP and non-CP MD were associated with lower HRQoL, even for children with less severe
129 difficulties and without other developmental impairments.

130 **What this study adds**

- 131 • Extremely preterm children with motor problems had lower health-related quality of
132 life.
- 133 • Clinically significant effects were observed for children with less severe difficulties.
- 134 • Effects were also found for children without motor-related healthcare use.
- 135 • These effects were less marked at higher quality of life percentiles.
- 136 • These heterogeneous associations raise questions for research about mitigating and
137 protective factors

138

139 **Key words:** Movement Assessment Battery for Children-2; movement difficulties; cerebral
140 palsy; extremely preterm; motor development; health-related quality of life; activities of
141 daily life

142 **Introduction**

143 Survival after extremely preterm (EPT, <28 weeks' gestational age (GA)) birth has increased in
144 recent decades with advances in obstetric and neonatal care,¹ but children born EPT continue
145 to face substantially higher risks of developmental problems and disorders than their term-
146 born peers.^{1,2} Motor disorders, comprising cerebral palsy (CP), developmental coordination
147 disorder (DCD) as well as other movement difficulties (MD) are common consequences of EPT
148 birth. The prevalence of CP is around 10% among children born EPT,³ and MD are present in
149 up to 50% of children without CP.⁴⁻⁷ While CP is clearly defined as a motor disorder with
150 established guidelines for health care provision,⁸⁻¹⁰ there is less agreement about whether all
151 children with MD should be classified as having a disorder. The low use of motor-related
152 health care (MRHC) services by EPT children with MD raises questions about whether this
153 reflects the absence of a health disorder or unmet need.¹¹

154 Impaired motor function can limit daily activities, schooling and social relationships, but the
155 consequences of CP and non-CP MD on children's lives and well-being are not well described.¹²
156 One approach to quantifying this impact is to measure health-related quality of life (HRQoL).
157 HRQoL evaluates the level of interference of health limitations in day-to-day functioning, by
158 considering the physical, emotional and social dimensions of health and well-being.¹³⁻¹⁵ A
159 systematic review by Zwicker et al.¹⁵ concluded that preschool-aged children born preterm or
160 with very low birth weight (<1500 grams) tend to have lower parent-reported HRQoL, whereas
161 evidence in school-aged children is scarce. However, these studies have not explored the
162 extent to which lower HRQoL is associated with specific prematurity-related developmental
163 comorbidities, including motor disorders or difficulties. Among children with CP or DCD in the
164 general population, studies generally report worse physical, psychosocial and social
165 functioning compared with typically developing peers.^{12,16}

166 This existing literature suggests that children's HRQoL is likely to be impacted by MD
167 associated with EPT birth, but these effects have not been studied and may be heterogeneous.
168 This study sought to measure the associations of CP and non-CP MD with HRQoL among
169 children born EPT with and without other neurodevelopmental impairments (NDI), and those
170 not receiving MRHC services.

171

172 **Methods**

173 ***Study Design and Participants***

174 This study uses data from the Screening to Improve Health in Very Preterm Infants in Europe
175 (SHIPS) population-based, prospective cohort of children born very preterm (VPT; <32 weeks'
176 GA) in 2011-2012 in 19 regions in 11 European countries.¹⁷ Data were collected from
177 obstetrical and neonatal records during the neonatal hospitalization, parental questionnaires
178 at two and five years of age and clinical assessments of neurocognitive and motor functioning
179 at five years of age for the sub-group of children born EPT. Our study population was limited
180 to this EPT sub-group.

181

182 ***Motor disorders and difficulties***

183 MD were assessed using the Movement Assessment Battery for Children-2nd edition (MABC-
184 2),¹⁸ a validated test previously used in high-risk populations such as children born EPT.⁵ It
185 considers performance on eight motor tasks in three domains: manual dexterity, aiming and
186 catching, and balance. All tasks are summed and converted to an age-adjusted percentile
187 score which allows the classification of results into: no MD (>15th percentile), at risk of MD (6-
188 15th percentile), and significant MD (\leq 5th percentile). As national norms are not existing in all
189 countries, we applied the United Kingdom norms, originally developed for the test and most
190 commonly used, to derive percentile scores for all children.^{18,19} The MABC-2 was administered
191 by trained psychologists or physiotherapists in local routine follow-up programs where
192 available (Belgium, the Netherlands, Sweden), or in the SHIPS research teams (other
193 countries). Common data collection guidelines and a core data collection form were
194 developed to standardize procedures and reporting.

195 Information on CP diagnosis was reported by parents in the five-year questionnaire, except
196 in France where CP diagnosis was ascertained during a medical visit.

197 We classified motor disorders and difficulties into four groups: children with CP were
198 considered a distinct group, as CP is a well-defined neurodevelopmental disorder with a
199 specific etiology,⁸ and children without CP were classified according to their MABC-2
200 percentiles. As the MABC-2 is not designed to assess movement abilities in children with

201 severe NDI,¹⁸ we excluded children with an intelligence quotient (IQ) <55 (<-3SD) or severe
202 hearing or visual impairment (**Figure 1**).

203

204 ***Health-related quality of life***

205 The child's HRQoL was measured using the parent-reported Pediatric Quality of Life
206 InventoryTM (PedsQL) generic core scales,²⁰ ages 5-7 years. This instrument has demonstrated
207 reliability and validity in healthy school populations, and in pediatric populations with acute
208 or chronic health conditions.^{21,22} It consists of 23 items with a 5-point Likert response scale in
209 four domains: physical (8 items), emotional (5 items), social (5 items) and school functioning
210 (5 items). Items were reverse-scored and linearly transformed to a 0 to 100 scale, with higher
211 scores indicating a better HRQoL.²⁰ Three summary scores are computed: the physical health
212 summary score (8 items on physical functioning), the psychosocial health summary score (15
213 items on emotional, social and school functioning), and the total score (23 items).

214

215 ***Covariables***

216 The following covariables were considered as potential confounders: child age and sex, and
217 family sociodemographic characteristics, including maternal age and parity at the child's birth,
218 maternal country of birth, parental cohabiting status, maternal educational level and
219 household unemployment status. For sub-group analyses, we used information on other NDI
220 including low full scale IQ and parent-reported hearing or visual impairment.

221

222 ***Analytic Approach***

223 We first described the characteristics of children included in the study sample and those
224 excluded because of missing MABC-2 or PedsQL scores. We compared the characteristics of
225 children by motor category (no MD, at risk of MD, significant MD, CP). Linear regression
226 analyses were used to measure associations between the motor categories and HRQoL,
227 adjusting for child age, sex and family sociodemographic characteristics. Because multiple
228 developmental impairments are frequent after EPT birth, and the association between these
229 impairments is not clear, we carried out sub-group analyses excluding children with a
230 moderate to severe NDI (IQ <70 (<-2SD) or hearing or visual impairment (implant or hearing

231 aid or deafness; blindness or difficulty seeing even with glasses)). We additionally excluded
232 children who were not receiving MRHC defined as having at least one visit during the past year
233 with a: (1) physiotherapist, motor development or psychomotor therapist, (2) occupational
234 therapist, or (3) early intervention specialist.¹¹ Then, among children without other moderate
235 to severe NDI, we explored possible differential effects over the HRQoL distribution using
236 quantile regression models.^{23,24} Lastly, to facilitate the interpretation of differences in scores,
237 given that measurements have no intrinsic clinical thresholds, we calculated the Cohen's δ as
238 a measure of the effect size, and used thresholds to interpret small (0.2), medium (0.5) and
239 large (0.8) effect size.²⁵

240

241 Loss to follow-up and missing data

242 We used inverse probability weighting (IPW) to take into account loss to follow-up.²⁶ As
243 previously described,⁷ characteristics of responders and non-responders were compared
244 (**Table S1**) and used to estimate the probability of response (**Table S2**). Missing data for
245 covariates were imputed using multiple imputation by chained equations for the weights
246 ($m=20$), and the final models ($m=20$).²⁷ Missing data were <2% for covariables in the final
247 models.

248 We did not impute data for children with missing MABC-2 or PedsQL scores as the missing at
249 random assumptions likely did not hold. However, for eligible children with missing MABC-2
250 data, neurodevelopmental specialists and an epidemiologist (RC, UA, SJ, and JZ) reviewed each
251 case. If a child was unable to complete a task/component because of severe motor
252 impairment, the lowest score on that particular scale was assigned. If data were missing for a
253 task in the absence of other developmental problems, the average of the other tasks was
254 assigned. In Belgium, some children had percentile scores from the MABC (1st edition) which
255 were used.²⁸ In all other cases, scores were left as missing.

256

257 Sensitivity analyses

258 Linear regression models were used for our main analysis, as these are most commonly used
259 in the HRQoL literature.^{29,30} However, these scores are not normally distributed because of
260 right censoring, due to bounded data at the maximum, and a left-skewed distribution
261 (**Figure S1**). We therefore verified whether use of alternative models (Tobit and the censored

262 least absolute deviations (CLAD) models) affected the estimates.^{31–33} Lastly, we reran final
263 models using unweighted and complete case samples and after excluding children with severe
264 NDI in the CP group (n=15), as this was an exclusion criterion for children without CP.
265 All analyses were carried out using the statistical software Stata version 15.0 (StataCorp,
266 College Station, TX, USA).

267

268 **Results**

269 Of 1,671 EPT infants alive at discharge, 1,654 survived to five years and 1,021 (61.7%) were
270 followed (**Figure 1**). One hundred children had a CP diagnosis (unweighted prevalence: 9.8%,
271 weighted prevalence: 11.1%). Among children without CP, 29 with severe NDI were excluded.
272 After excluding missing MABC-2 and PedsQL measures, the final sample comprised 810
273 children.

274 Children were assessed at 5.6 (0.4) years (mean (SD)) (**Table 1**); 29.5% were born <26 weeks'
275 GA, 51.6% were males and 72.5% were singletons. Their mothers were aged 35 years or more
276 for 26.7%, 58.9% were primiparous, 37.3% had at least a bachelor's degree and 18.6% were
277 born outside of Europe. As loss to follow-up was mainly related to social disadvantage
278 (**Table S1**), IPW affected the distribution of most sociodemographic characteristics.

279 Younger maternal age and not breastfeeding were associated with missing MABC-2 (n=116)
280 and PedsQL scores (n=63) (**Tables S3-S4**). Missing PedsQL was also more frequent among
281 multiparous and non-European mothers.

282 The proportion of males increased with the severity of MD and was highest among children
283 with CP (**Table 2**). Children without MD and those at risk of MD had mothers with similarly
284 distributed educational levels, while those with significant MD or CP were more likely to have
285 mothers with lower education. A larger proportion of household unemployment was observed
286 for all children with MD or CP in comparison with children without MD. 25.3% and 16.2% of
287 children with CP had severe and moderate NDI, respectively; for analyses of MD, severe NDI
288 were excluded, but moderate NDI increased with MD severity.

289 Compared to children without MD, those at risk of MD, with significant MD and CP had lower
290 PedsQL total scores (Beta and 95% confidence intervals (β [95% CI])): -5.5 [-8.2, -2.7], -9.8 [-
291 12.8, -6.8], and -26.7 [-31.6, -21.8], respectively (**Table 3**). Decreases were greater for physical
292 than for psychosocial scores. Models adjusted on sociodemographic characteristics provided

293 similar results. After exclusion of children with moderate to severe NDI (n=123), associations
294 with the PedsQL total score were slightly attenuated, particularly for the CP group. Finally,
295 among these children, those not receiving MRHC services had higher PedsQL scores than those
296 receiving services. However, they still had lower PedsQL total scores than children without
297 MD. Children with CP were not included in this analysis because almost all received MRHC
298 services. When these estimates were converted to Cohen's δ (Table S5), they were in the
299 range of 0.31-0.41, 0.38-0.60, 1.16-1.61 for at risk of MD, significant MD and CP, respectively.
300 In quantile analyses, the estimated declines in PedsQL score for children at risk or with
301 significant MD in comparison to children with no MD widened with decreasing quantiles, with
302 non-significant decreases at the 90th percentile, but up to 15.4 points for the 10th percentile
303 (Figure 2). In contrast, children with CP had lower scores for all quantiles. Similar patterns
304 were observed for physical and psychosocial scores (Figures S2-S3).
305 Analysis using censored regression Tobit and CLAD models did not show appreciable
306 differences with linear models (Table S6). For instance, total score reductions for significant
307 MD were -9.1 [-12.0, -6.1], -8.1 [-10.8, -5.4] and -9.2 [-13.6, -6.2] for linear, Tobit and CLAD
308 models respectively. One difference, however, was a smaller reduction of the physical score
309 for the at-risk category in the CLAD model compared to linear and Tobit models. Linear
310 regressions using the unweighted and complete case samples, and excluding children with a
311 severe NDI (n=15) in the CP group, yielded similar conclusions, although in the latter analysis,
312 scores were slightly higher for children with CP.

313

314 **Discussion**

315 ***Summary of findings***

316 Motor disorders and difficulties were associated with poorer HRQoL among EPT children aged
317 five years, with the lowest level for children with CP, followed by those with significant MD
318 and at risk of MD compared with children with no MD. Decreases were greater for physical
319 than psychosocial scores. They were also more pronounced at lower HRQoL percentiles for
320 children at risk of MD or with significant MD, whereas decreases were observed at all
321 percentiles for children with CP. Differences persisted after exclusion of children with
322 moderate to severe NDI and those not receiving any MRHC services over the past year.

323

324 ***Comparison with the published literature***

325 The results from this European multi-regional cohort, one of the largest with information on
326 HRQoL and MD,^{12,15,34} are consistent with the literature on DCD where most studies have
327 reported worse physical, psychological and social functioning in children with DCD compared
328 with peers.^{12,35} Specifically among children born VPT, 11-year-old children with DCD (defined
329 as MABC-2 score $\leq 5^{\text{th}}$ percentile) self-reported lower HRQoL than children born VPT without
330 motor impairment;³⁶ and children aged 6-10 years with global developmental disability and
331 CP had reduced parent-reported HRQoL.³⁷ Studies that used $\leq 15^{\text{th}}$ percentile as the MABC cut-
332 off score to indicate DCD, suggest that children in the "border-line" range for motor function
333 experience significant reductions in HRQoL, in line with our findings for the at-risk group.¹²
334 Among children with CP, Makris et al.¹⁶ reported worse physical functioning compared with
335 typically developing peers, but results have been less clear concerning psychosocial
336 functioning, whereas we observed decreases in all domains.

337

338 ***Interpretation***

339 There were marked differences in HRQoL scores between children with CP and those with
340 non-CP MD, although they were less striking once children with other NDI were excluded. We
341 did not have information on the type and severity of CP, which would be needed to further
342 understand results in the CP group.³⁸ The fact that HRQoL scores followed a gradient reflecting
343 the severity of reduced motor function provides support for a direct association, but
344 interpreting the scores is complex. In particular, a key question concerns the threshold
345 indicating a clinically meaningful decrease.³⁹⁻⁴¹ Other studies on HRQoL have regarded
346 differences of 5 to 10 points on a 100-point scale as clinically significant.⁴² Hilliard et al.³⁹
347 established that the amount of change that children and young people with diabetes and their
348 parents perceive as meaningful in everyday functioning or activities was between 4.5 and 6.5
349 points of the PedsQL score.³⁹ This result is of same order of magnitude as the difference
350 between children with and without health problems found in the initial PedsQL validation
351 study and corresponds to the effect found for children at risk of MD and without NDI in our
352 study.²⁰ Our calculations with the Cohen's δ were also consistent with this interpretation.
353 Another question relates to the validity of parent-reported HRQoL with differences existing
354 between self- and parental-report of the child's HRQoL.^{15,43} Compared to other quality of life

355 measures, the PedsQL instrument, focuses on the child's functional status,⁴⁴ with better
356 agreement between parents and children on observable items than measures focusing on
357 feelings and lived-experiences.^{34,43} Given the young age of the children and the high
358 prevalence of NDI in this study, self-report was not appropriate,³⁴ but future research should
359 assess whether parents' characteristics or beliefs contribute to the variation in HRQoL and
360 confirm these findings using self-reported HRQoL.

361

362 ***Implications for clinical practice, policy and research***

363 Early interventions to improve motor function in children born preterm and/or with DCD are
364 effective and efficient.⁴⁵⁻⁴⁸ These results showing consequences of motor disorders on EPT
365 children's HRQoL at five-years of age therefore highlight the importance of early screening
366 and support. These findings also reinforce calls for continued follow-up of children born EPT
367 beyond two years and for better diagnosis and health service provision for children at risk of
368 MD or with significant MD,⁴⁹ in particular for children without other developmental problems
369 who may be less likely to receive MRHC services.¹¹

370 Analyses using quantile regression illustrated a heterogeneous association of MD with HRQoL
371 and suggests that there may be mitigating or protective factors that preserve HRQoL for some
372 children.^{23,24} Future studies should focus on identifying protective individual, familial or
373 broader environmental factors, as these may lead to more effective interventions and better
374 identification of children requiring more support.⁵⁰ Using integrated measures of day-to-day
375 functioning, such as the PedsQL, for research alongside more traditional neurodevelopmental
376 measures opens up new opportunities for discovery and responds to families' concerns about
377 their EPT child's overall well-being.⁵¹

378

379 ***Strengths and limitations***

380 The main strengths of this study are its large, population-based sample of >800 children born
381 EPT with standardized collection of data on motor function and HRQoL using validated
382 instruments. CP was based on a parental-report of a clinical diagnosis, which may lead to some
383 misclassification, although almost all children with CP will have received a diagnosis by age
384 five in cohorts with high health service use,^{52,53} such as ours.⁵⁴ This is supported by the CP
385 prevalence of 11% which is in the range of recent cohort studies (9-12%).^{3,55,56} However,

386 analysis of the type and severity of CP on HRQoL was not possible. We carried out sub-group
387 analyses excluding children with moderate to severe NDI to assess the association between
388 motor problems and HRQoL in the absence of these impairments. However, EPT children
389 experience a range of developmental comorbidities that may affect their HRQoL. How other
390 health and developmental conditions interact with CP and non-CP MD to affect HRQoL is an
391 important area for future research. Finally, there may be bias from loss to follow-up, but
392 information was available on factors affecting attrition, which were primarily related to social
393 disadvantage, and IPW corrected for characteristics under-represented in the follow-up
394 sample.

395

396 **Conclusion**

397 Motor disorders and difficulties were associated with lower HRQoL at five years of age, even
398 when they were less severe. These results illustrate the importance of follow-up and health
399 service provision for EPT children across the full spectrum of motor problems in order to
400 reduce their impact on HRQoL.

401 **Supplemental Tables:**

402 **1/ Table S1:** Characteristics of children followed and lost to follow-up at 5 years of age
403 (without IPW).

404 **2/ Table S2:** List of the variables included in the multiple imputation by chained equations and
405 IPW programs.

406 **3/ Table S3:** Characteristics of children included in the study with a MABC-2 score and
407 comparison with children without MABC-2 score and without CP (without IPW).

408 **4/ Table S4:** Characteristics of children included in the study and comparison with children
409 without PedsQL score (without IPW).

410 **5/ Table S5:** Unadjusted associations of PedsQL scores with motor category for children
411 without other moderate to severe NDI expressed in Cohen's δ effect size (standardized mean
412 difference).

413 **6/ Table S6:** Adjusted association of PedsQL scores with motor category – Sensitivity analyses
414 with the use of censored regression models; in complete case without IPW, complete case
415 with IPW, and multiple imputed dataset without IPW; and with the exclusion of children with
416 a severe NDI in the CP group.

417

418 **Supplemental Figures:**

419 **1/ Figure S1:** Distribution of PedsQL scores.

420 **2/ Figure S2:** Adjusted associations of PedsQL quantiles (physical score) with motor category
421 for children without other moderate to severe NDI.

422 **3/ Figure S3:** Adjusted associations of PedsQL quantiles (psychosocial score) with motor
423 category for children without other moderate to severe NDI.

424

425 **Data sharing:**

426 The dataset analysed during the current study are not publicly available due to health data
427 protection but are available from the corresponding author on reasonable request.

428

Supplementary materials:

Ethical approval:

All study regions obtained ethical approval according to national legislations. The study was also approved by the French Advisory Committee on Use of Health Data in Medical Research (CCTIRS) and the French National Commission for Data Protection and Liberties (CNIL). Parents gave their written informed consent to participating in the study prior to any data collection.

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References

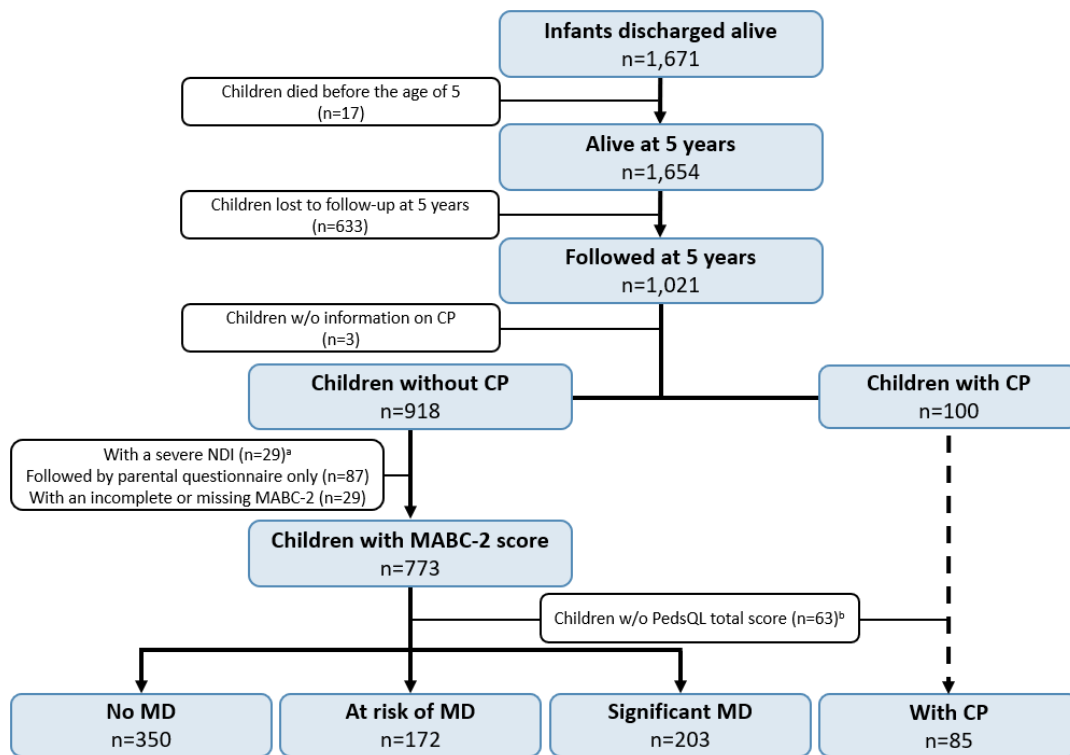
1. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. *JAMA*. 2015 Sep 8;314(10):1039–51.
2. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet Lond Engl*. 2008 Jan 19;371(9608):261–9.
3. Himpens E, Van den Broeck C, Oostra A, Calders P, Vanhaesebrouck P. Prevalence, type, distribution, and severity of cerebral palsy in relation to gestational age: a meta-analytic review. *Dev Med Child Neurol*. 2008 May;50(5):334–40.
4. Williams J, Lee KJ, Anderson PJ. Prevalence of motor-skill impairment in preterm children who do not develop cerebral palsy: a systematic review. *Dev Med Child Neurol*. 2010;52(3):232–7.
5. de Kieviet JF, Piek JP, Aarnoudse-Moens CS, Oosterlaan J. Motor development in very preterm and very low-birth-weight children from birth to adolescence: a meta-analysis. *JAMA*. 2009 Nov 25;302(20):2235–42.
6. Edwards J, Berube M, Erlandson K, Haug S, Johnstone H, Meagher M, et al. Developmental coordination disorder in school-aged children born very preterm and/or at very low birth weight: a systematic review. *J Dev Behav Pediatr JDBP*. 2011 Nov;32(9):678–87.
7. Aubert AM, Costa R, Ådén U, Cuttini M, Männamaa M, Pierrat V, et al. Movement Difficulties at Age Five Among Extremely Preterm Infants. *Pediatrics*. 2022 May 26;e2021054920.
8. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl*. 2007 Feb;109:8–14.

9. Agency for Clinical Innovation. Management Of Cerebral Palsy In Children: A Guide For Allied Health Professionals [Internet]. 2018 [cited 2022 Jun 27] p. 148. Available from: https://www1.health.nsw.gov.au/pds/ActivePDSDocuments/GL2018_006.pdf
10. National Institute for Health and Care Excellence. Cerebral palsy in under 25s: assessment and management [Internet]. NICE; 2017 [cited 2022 Jun 27] p. 48. Available from: <https://www.nice.org.uk/guidance/NG62>
11. Costa R, Aubert AM, Seppänen AV, Ådén U, Sarrechia L, Zemlin M, et al. Motor-related health care for 5-year-old children born extremely preterm with movement impairments. *Dev Med Child Neurol*. 2022 Mar 17;
12. 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 Jul;39(4):562–80.
13. Eiser C. Use of quality of life measures in clinical trials. *Ambul Pediatr Off J Ambul Pediatr Assoc*. 2004 Aug;4(4 Suppl):395–9.
14. Mottram R, Holt J. “Is gestational age a factor in determining the health-related quality of life of children and young people born preterm?” A critical review of the literature. *J Neonatal Nurs*. 2010 Apr 1;16(2):80–90.
15. 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 Feb;121(2):e366-376.
16. Makris T, Dorstyn D, Crettenden A. Quality of life in children and adolescents with cerebral palsy: a systematic review with meta-analysis. *Disabil Rehabil*. 2021 Feb;43(3):299–308.
17. Zeitlin J, Maier RF, Cuttini M, Aden U, Boerch K, Gadzinowski J, et al. Cohort Profile: Effective Perinatal Intensive Care in Europe (EPICE) very preterm birth cohort. *Int J Epidemiol*. 2020 Apr 1;49(2):372–86.
18. Henderson SE, Sugden DA, Barnett AL. Movement Assessment Battery for Children-2 (2nd ed.). Psychological corporation. London, United Kingdom; 2007.
19. Costa R, Johnson S, Cuttini M, Pierrat V, Sarrechia I, Barros H, et al. The impact of choice of norms on classification of motor impairment for children born very preterm. *Early Hum Dev*. 2020 May 7;105056.
20. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care*. 2001 Aug;39(8):800–12.
21. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr Off J Ambul Pediatr Assoc*. 2003 Dec;3(6):329–41.
22. Varni JW, Burwinkle TM, Berrin SJ, Sherman SA, Artavia K, Malcarne VL, et al. The PedsQL in pediatric cerebral palsy: reliability, validity, and sensitivity of the Generic Core Scales and Cerebral Palsy Module. *Dev Med Child Neurol*. 2006 Jun;48(6):442–9.
23. Koenker R. Quantile regression. Cambridge University Press; 2005.
24. Petscher Y, Logan JAR. Quantile regression in the study of developmental sciences. *Child Dev*. 2014 Jun;85(3):861–81.
25. Cohen J. Statistical power analysis for the behavioral sciences [Internet]. Vol. Second Edition. New York University: Lawrence Erlbaum Associates; 1988. Available from: <http://www.utstat.toronto.edu/~brunner/oldclass/378f16/readings/CohenPower.pdf>

26. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res.* 2013 Jun;22(3):278–95.
27. Seaman SR, White IR, Copas AJ, Li L. Combining Multiple Imputation and Inverse-Probability Weighting. *Biometrics.* 2012;68(1):129–37.
28. Henderson SE, Sugden DA. *Movement Assessment Battery for Children.* Psychological corporation. London, United Kingdom; 1992.
29. Ferreira PL, Ferreira LN, Pereira LN. How consistent are health utility values? *Qual Life Res Int J Qual Life Asp Treat Care Rehabil.* 2008 Sep;17(7):1031–42.
30. Wong ELY, Cheung AWL, Wong AYK, Xu RH, Ramos-Goñi JM, Rivero-Arias O. Normative Profile of Health-Related Quality of Life for Hong Kong General Population Using Preference-Based Instrument EQ-5D-5L. *Value Health J Int Soc Pharmacoeconomics Outcomes Res.* 2019 Aug;22(8):916–24.
31. Wells CS, Hintze JM. Dealing with assumptions underlying statistical tests. *Psychol Sch.* 2007;44(5):495–502.
32. Wilhelm MO. Practical Considerations for Choosing Between Tobit and SCLS or CLAD Estimators for Censored Regression Models with an Application to Charitable Giving*. *Oxf Bull Econ Stat.* 2008;70(4):559–82.
33. Austin PC, Escobar M, Kopec JA. The use of the Tobit model for analyzing measures of health status. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil.* 2000;9(8):901–10.
34. Vieira MEB, Linhares MBM. Quality of life of individuals born preterm: a systematic review of assessment approaches. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil.* 2016 Sep;25(9):2123–39.
35. 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.* 2019 Jan;84:85–95.
36. Uusitalo K, Haataja L, Nyman A, Ripatti L, Huhtala M, Rautava P, et al. Preterm children’s developmental coordination disorder, cognition and quality of life: a prospective cohort study. *BMJ Paediatr Open.* 2020;4(1):e000633.
37. Berbis J, Einaudi MA, Simeoni MC, Brévaut-Malaty V, Auquier P, d’Ercole C, et al. Quality of life of early school-age French children born preterm: a cohort study. *Eur J Obstet Gynecol Reprod Biol.* 2012 May;162(1):38–44.
38. Arnaud C, White-Koning M, Michelsen SI, Parkes J, Parkinson K, Thyen U, et al. Parent-reported quality of life of children with cerebral palsy in Europe. *Pediatrics.* 2008 Jan;121(1):54–64.
39. Hilliard ME, Lawrence JM, Modi AC, Anderson A, Crume T, Dolan LM, et al. Identification of minimal clinically important difference scores of the PedsQL in children, adolescents, and young adults with type 1 and type 2 diabetes. *Diabetes Care.* 2013 Jul;36(7):1891–7.
40. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol Off J Am Soc Clin Oncol.* 1998 Jan;16(1):139–44.
41. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol.* 2003 May;56(5):395–407.
42. Fayers P, Machin D. *Quality of Life: The assessment, analysis and interpretation of patient-reported outcomes* [Internet]. John Wiley & Sons; 2007 [cited 2022 Apr 28]. Available from: <https://abdn.pure.elsevier.com/en/publications/quality-of-life-the-assessment-analysis-and-interpretation-of-pat>

43. Upton P, Lawford J, Eiser C. Parent-child agreement across child health-related quality of life instruments: a review of the literature. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil*. 2008 Aug;17(6):895–913.
44. Waters E, Davis E, Ronen GM, Rosenbaum P, Livingston M, Saigal S. Quality of life instruments for children and adolescents with neurodisabilities: how to choose the appropriate instrument. *Dev Med Child Neurol*. 2009 Aug;51(8):660–9.
45. Doyle LW, Anderson PJ, Battin M, Bowen JR, Brown N, Callanan C, et al. Long term follow up of high risk children: who, why and how? *BMC Pediatr*. 2014 Nov 17;14:279.
46. Spittle AJ, Orton J, Anderson PJ, Boyd R, Doyle LW. Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. *Cochrane Database Syst Rev*. 2015 Nov 24;(11):CD005495.
47. Smits-Engelsman B, Blank R, van der Kaay AC, Mosterd-van der Meijs R, Vlugt-van den Brand E, Polatajko HJ, et al. Efficacy of interventions to improve motor performance in children with developmental coordination disorder: a combined systematic review and meta-analysis. *Dev Med Child Neurol*. 2013 Mar;55(3):229–37.
48. Harris SR, Mickelson ECR, Zwicker JG. Diagnosis and management of developmental coordination disorder. *CMAJ Can Med Assoc J J Assoc Medicale Can*. 2015 Jun 16;187(9):659–65.
49. European Foundation for the Care of Newborn Infants. European Standards of Care for Newborn Health. [Internet]. 2018 [cited 2022 May 30]. Available from: https://www.efcni.org/wp-content/uploads/2018/11/2018_11_16_ESCNH_Report_final.pdf
50. Pereira S, Bastos F, Santos C, Maia J, Tani G, Robinson LE, et al. Variation and Predictors of Gross Motor Coordination Development in Azorean Children: A Quantile Regression Approach. *Int J Environ Res Public Health*. 2022 Apr 29;19(9):5417.
51. Roberts G. Quality of life after extremely preterm birth. *Arch Dis Child*. 2019 Apr;104(4):311–2.
52. McIntyre S, Morgan C, Walker K, Novak I. Cerebral palsy--don't delay. *Dev Disabil Res Rev*. 2011;17(2):114–29.
53. Gorter JW, Ketelaar M, Rosenbaum P, Hadders PJM, Palisano R. Use of the GMFCS in infants with CP: the need for reclassification at age 2 years or older. *Dev Med Child Neurol*. 2009 Jan;51(1):46–52.
54. Seppänen AV, Draper ES, Petrou S, Barros H, Aubert AM, Andronis L, et al. High Healthcare Use at Age 5 Years in a European Cohort of Children Born Very Preterm. *J Pediatr*. 2022 Apr;243:69-77.e9.
55. Hafström M, Källén K, Serenius F, Maršál K, Rehn E, Drake H, et al. Cerebral Palsy in Extremely Preterm Infants. *Pediatrics*. 2018 Jan;141(1):e20171433.
56. Pierrat V, Marchand-Martin L, Marret S, Arnaud C, Benhammou V, Cambonie G, et al. Neurodevelopmental outcomes at age 5 among children born preterm: EPIPAGE-2 cohort study. *BMJ*. 2021 Apr 28;373:n741.
57. UNESCO Institute for Statistics. International standard classification of education: ISCED 2011 [Internet]. Montreal, Quebec: UNESCO Institute for Statistics; 2012. Available from: <http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-isced-2011-en.pdf>

Figure 1. Flowchart of the sample selection from the EPICE-SHIPS' cohort (children born <28 weeks' gestational age).



Abbreviations: w/o, without. CP, cerebral palsy. NDI, neurodevelopmental impairment. MABC-2, Movement Assessment Battery for Children – 2nd Edition. PedsQL, Pediatric Quality of Life Inventory™. MD, movement difficulties.

^aNeurodevelopmental impairment (NDI) integrated cognitive, hearing and visual impairment. Severe NDI defined as an intelligence quotient (IQ) <55 (<-3SD), deafness or difficulties hearing even with hearing aids or implants or blindness or seeing light only.

^bIncluded the exclusion of 16 children in the category no MD, 11 in the category at risk of MD, 21 in the category significant MD, and 15 in the category CP.

Table 1. Characteristics of children included in the study with and without IPW (N=810).

	Without IPW		With IPW	
	N	%	N	%
Child characteristics				
Age at assessment in years, mean (SD)	5.6	(0.3)	5.6	(0.4)
Male sex	409	50.5	418	51.6
Sociodemographic characteristics				
Maternal age at childbirth (years)				
<25	88	10.9	127	15.8
25-34	473	58.7	464	57.5
≥35	245	30.4	215	26.7
Parental cohabiting status (single/other)	118	14.6	124	15.3
Maternal educational level				
Low education ISCED 0-2	137	17.1	147	18.4
Intermediate education ISCED 3-5	346	43.3	354	44.3
High education ISCED 6-8	316	39.5	298	37.3
Household unemployment status (at least one parent unemployed)	101	12.6	116	14.4
Primiparous (at child's birth)	487	61.0	471	58.9
Maternal country of birth				
Native-born	639	79.2	599	74.3
Other European country	51	6.3	58	7.1
Non-European country	117	14.5	150	18.6
Perinatal and neonatal characteristics				
Gestational age (completed weeks)				
≤24	85	10.5	96	11.8
25	152	18.8	143	17.7
26	239	29.5	231	28.5
27	334	41.2	340	42.0
Small for gestational age				
<3 rd percentile	123	15.2	112	13.8
3 rd -9 th percentile	70	8.6	67	8.3
≥10 th percentile	617	76.2	631	77.9
Multiple birth	234	28.9	223	27.5
Congenital anomaly	66	8.1	63	7.7
Severe neonatal morbidity ^a	194	24.4	212	26.6
Bronchopulmonary dysplasia ^b	274	34.4	291	36.6
Breastfeeding at discharge	464	58.4	428	53.8
Country (region)				
Belgium (Flanders)	51	6.3	59	7.3
Denmark (Eastern Region)	42	5.2	48	6.0
Estonia (entire country)	34	4.2	22	2.7
France (Burgundy, Ile-de-France, Northern Region)	156	19.3	135	16.6
Germany (Hesse, Saarland)	59	7.3	87	10.7
Italy (Emilia-Romagna, Lazio, Marche)	136	16.8	110	13.6
The Netherlands (Central Eastern)	63	7.8	46	5.6
Poland (Wielkopolska)	39	4.8	31	3.8
Portugal (Lisbon, Northern Region)	96	11.9	83	10.2
The United Kingdom (East Midlands, Northern, Yorkshire and the Humber)	102	12.6	161	19.8
Sweden (Greater Stockholm)	32	4.0	30	3.7

Abbreviations: IPW, inverse probability weighting. SD, standard deviation. ISCED, International Standard Classification of Education.⁵⁷

Values are frequencies (Ns rounded to a whole number), percentages (% excluding missing values and rounded to one decimal), and mean (SD) for continuous variables, all without and with the use of inverse probability weighting (IPW) to correct for loss to follow-up.

^aIncluded intraventricular haemorrhage grade III/IV, cystic periventricular leukomalacia, retinopathy of prematurity stage III or more, and surgical necrotizing enterocolitis.

^bDefined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.

Table 2. Sample characteristics by motor category.

	No MD		Non-CP MD				CP	
	N	%	At risk of MD		Significant MD		N	%
	N	%	N	%	N	%	N	%
Child characteristics								
Age at assessment in years, mean (SD)	5.6	(0.3)	5.6	(0.4)	5.6	(0.3)	5.6	(0.5)
Child sex								
Male	136	41.1	87	52.7	131	60.5	65	65.5
Female	195	58.9	78	47.3	86	39.5	34	34.5
Neurodevelopmental impairment^a								
None	247	74.9	89	54.1	68	31.2	24	24.2
Mild	75	22.6	69	41.9	88	40.7	34	34.4
Moderate	8	2.5	7	4.0	61	28.2	16	16.2
Severe	-	-	-	-	-	-	25	25.3
Family sociodemographic characteristics								
Maternal age at childbirth (years)								
<25	29	8.8	26	16.3	45	20.5	27	28.4
25-34	197	59.5	103	63.9	117	53.7	47	48.5
≥35	105	31.6	32	19.8	56	25.8	22	23.0
Parental cohabiting status								
Married/Couple/Cohabiting	281	85.0	135	81.7	186	86.6	84	84.4
Single/Other	50	15.0	30	18.3	29	13.4	15	15.6
Maternal educational level								
Low education ISCED 0-2	51	15.7	27	16.8	49	22.3	20	21.8
Intermediate education ISCED 3-5	141	43.4	69	42.4	99	45.5	44	48.2
High education ISCED 6-8	134	40.9	67	40.9	70	32.1	28	30.0
Household unemployment status								
Employed or other situation ^b	300	91.3	133	81.5	176	82.7	76	79.0
At least one parent unemployed	29	8.7	30	18.5	37	17.3	20	21.0
Parity								
Primiparous	179	55.0	110	67.7	139	64.7	43	44.4
Multiparous	146	45.0	52	32.3	76	35.3	54	55.6
Maternal country of birth								
Native-born	243	73.9	131	80.0	156	71.8	71	71.4
European born	21	6.4	14	8.5	19	8.7	4	4.0
Non-European born	65	19.7	19	11.5	42	19.5	24	24.7

Abbreviations: MD, movement difficulties. SD, standard deviation. ISCED, International Standard Classification of Education.⁵⁷

Values are weighted frequencies (Ns rounded to a whole number), percentages (% excluding missing values and rounded to one decimal), and mean (SD) for continuous variables, all with the use of inverse probability weighting (IPW) to correct for loss to follow-up.

^aNeurodevelopmental impairment integrated cognitive, hearing and visual impairment. Mild impairment defined as an intelligence quotient (IQ) between 84 and 70 (-1 standard deviation (SD) to -2 SD), difficulties hearing not requiring hearing aids or implants or glasses but seeing well when wearing them. Moderate impairment defined as an IQ between 69 and 55 (-2 SD to -3 SD), hearing aids or implants but hearing well when wearing them or difficulties seeing even wearing glasses. Severe impairment defined as an IQ <55 (<-3 SD), deafness or difficulties hearing even with hearing aids or implants or blindness or seeing light only.

^bOther situations included student, parental leave, home parent and other.

Table 3. Unadjusted and adjusted association of PedsQL scores with motor category (N=810).

		n ^a	PedsQL Physical Health Summary Score β [95% CI] ^b	PedsQL Psychosocial Health Summary Score β [95% CI]	PedsQL Total Scale Score β [95% CI]
Main analysis (N=810)					
Adjusted on child age and sex	No MD	330	REF	REF	REF
	At risk of MD	165	-5.6 [-9.3, -1.9]	-5.5 [-8.2, -2.7]	-5.5 [-8.2, -2.7]
	Significant MD	216	-12.5 [-16.7, -8.3]	-8.2 [-11.1, -5.2]	-9.8 [-12.8, -6.8]
	CP	99	-35.9 [-43.6, -28.1]	-21.2 [-25.8, -16.7]	-26.7 [-31.6, -21.8]
& Adjusted on family sociodemographic characteristics^c	No MD	330	REF	REF	REF
	At risk of MD	165	-5.4 [-9.1, -1.6]	-4.9 [-7.6, -2.1]	-5.0 [-7.7, -2.3]
	Significant MD	216	-11.9 [-16.1, -7.8]	-7.4 [-10.3, -4.5]	-9.1 [-12.0, -6.1]
	CP	99	-35.3 [-42.7, -27.9]	-20.6 [-25.2, -16.0]	-26.1 [-31.0, -21.2]
Sub-group analysis – After exclusion of children with other moderate to severe NDI (N=687)^d					
Adjusted on child age and sex and family sociodemographic characteristics	No MD	325	REF	REF	REF
	At risk of MD	161	-6.0 [-9.8, -2.2]	-5.6 [-8.4, -2.9]	-5.7 [-8.5, -3.0]
	Significant MD	156	-11.5 [-16.1, -7.0]	-6.0 [-9.1, -2.8]	-8.1 [-11.3, -4.8]
	CP	44	-20.5 [-28.6, -12.3]	-13.9 [-19.1, -8.7]	-16.2 [-21.6, -10.8]
Sub-group analysis – After exclusion of children with other developmental difficulties and stratified on receipt of motor-related health care (N=638)^e					
No (n=507)	No MD	282	REF	REF	REF
	At risk of MD	123	-5.1 [-9.4, -0.8]	-4.3 [-7.5, -1.2]	-4.6 [-7.7, -1.4]
	Significant MD	102	-8.9 [-14.0, -3.9]	-3.1 [-6.6, 0.4]	-5.2 [-8.8, -1.7]
Yes (n=131)	No MD	40	REF	REF	REF
	At risk of MD	39	-10.1 [-18.0, -2.1]	-6.1 [-12.7, 0.6]	-7.4 [-13.7, -1.0]
	Significant MD	53	-17.4 [-26.2, -8.6]	-7.7 [-15.1, -0.2]	-11.4 [-18.6, -4.3]

Abbreviations: PedsQL, Pediatric Quality of Life Inventory™. β, Beta. CI, confidence interval. MD, movement difficulties. REF, reference category. CP, cerebral palsy. NDI, neurodevelopmental impairment.

^aWeighted frequencies (Ns rounded to a whole number).

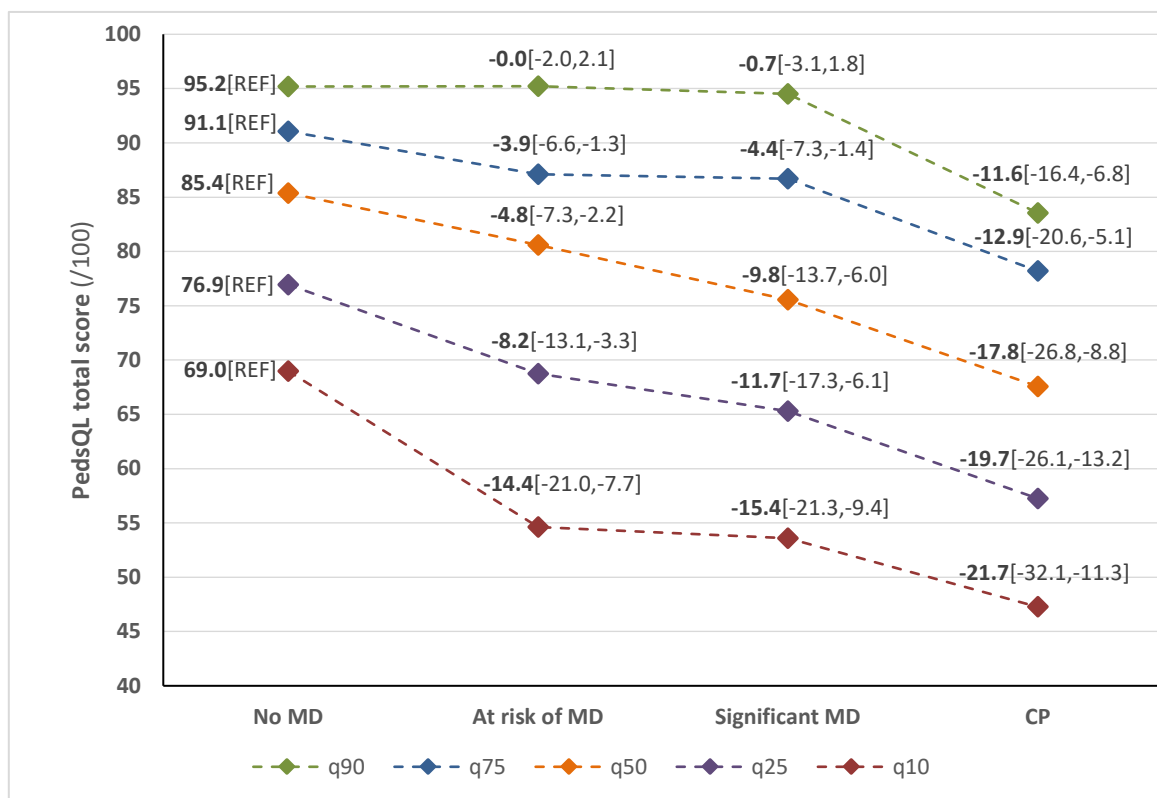
^bPedsQL score reductions expressed in Beta and their 95% confidence intervals (β [95% CI]) with the use of inverse probability weighting (IPW) to correct for loss to follow-up.

^cMaternal age and parity at childbirth, maternal country of birth, parental cohabiting status, maternal educational level and household unemployment status.

^dChildren with moderate to severe cognitive (full scale intelligence quotient (IQ) <70 (<-2SD)), hearing or visual impairment (implant or hearing aid or deafness; blindness or difficulty seeing even with glasses).

^eReceiving motor-related health care was defined as having at least one visit during the last 12 months to any of the following: (1) physiotherapist, motor development or psychomotor therapist, or kinesiologist; (2) occupational therapist, or (3) early intervention specialist.¹¹

Figure 2. Adjusted associations of PedsQL quantiles (total score) with motor category for children without other moderate to severe NDI.



Abbreviations: PedsQL, Pediatric Quality of Life Inventory™. REF, reference category. MD, movement difficulties. CP, cerebral palsy. q90, quantile 90; q75, quantile 75; q50, quantile 50; q25, quantile 25; q10, quantile 10.

PedsQL total score [REF] and reductions expressed in Beta and their 95% confidence intervals (β [95% CI]) rounded to one decimal, all with the use of inverse probability weighting (IPW) to correct for loss to follow-up; adjustment on child age and sex, and family sociodemographic characteristics including maternal age and parity at childbirth, maternal country of birth, parental cohabiting status, maternal educational level and household unemployment status; and exclusion of children with a moderate to severe neurodevelopmental impairment (NDI) (cognitive (full scale intelligence quotient (IQ) <70 (<-2SD)), hearing or visual impairment (implant or hearing aid or deafness; blindness or difficulty seeing even with glasses)).

As illustrative example, for the quantile 50 (q50), the reference value (category no MD) is 85.4 and we observed reductions of the PedsQL total score expressed in Beta and their 95% confidence intervals (β [95% CI]) of -4.8 [-7.3, -2.2], -9.8 [-13.7, -6.0] and -17.8 [-26.8, -8.8] for the categories at risk of MD, significant MD and CP, respectively, in comparison to the reference category.

8.1. Synthesis of principal results

The first two studies in this doctoral work confirmed the high prevalence of CP among children born EPT, approximately one out of 10 children, as well as of non-CP MD, with about 50% of our European sample of children without CP being classified as at-risk or having significant MD when tested with the MABC-2. Secondly, we found multiple clinical and sociodemographic risk factors which identified children at higher risk of MD. There were similarities in some of the risk factors associated with both non-CP MD and CP, but risk factor profiles were different, which is indicative of the probable distinct aetiologies of non-CP MD and CP. We reinforced knowledge on the different clinical risk factors for CP, with strong associations found with brain lesions and other neonatal morbidities. Several clinical factors were also associated with non-CP MD but with a lower order of magnitude for most of them. As hypothesized, sociodemographic risk factors were consistently associated with non-CP MD, while these associations were less marked compared to CP. This point illustrates the importance of integrating social circumstances into public health programmes for children born EPT. Lastly, we observed important differences in prevalence of MD between countries which persisted after adjustment for population characteristics.

Our third study focused on the care of children with developmental motor problems, those receiving MRHC services and the factors associated with the reception of services. We found that with the exception of children with CP, where MRHC service use over the past year was almost 90%, the majority of children with non-CP MD were not receiving MRHC services, with important variation between countries. In particular, children without other developmental difficulties were the least likely to receive MRHC services. These results illustrate the need for the establishment of national and international guidelines for the support of children born EPT during their first years of life – even if they do not have already recognized impairments – in line with recent recommendations by the European Foundation of the Care of Newborn Infants (European Foundation for the Care of Newborn Infants, 2018; Orton et al., 2018). They also suggest that health care professionals may need additional training to detect developmental motor problems (Camden et al., 2015; Harris et al., 2015). Finally, these results may reflect that parents and/or health professionals do not perceive the child's difficulties as being significant problems requiring intervention (Missiuna et al., 2006).

This last possibility and the very high prevalence of these developmental motor problems provides the context for the fourth study in this doctoral work to measure the daily consequences of CP and non-CP MD among children born EPT for all children, but also children who were not receiving MRHC. This is important because access to needed healthcare services has been associated with clinically meaningful positive changes in HRQoL (Seid et al., 2006). Our analysis of the association between CP and non-CP MD and the child's HRQoL found that developmental motor problems were associated with poorer HRQoL, with the lowest level for children with CP, followed by those with significant MD and at risk for MD, in comparison to EPT children without MD.

For children with CP, decreases were observed at all quantiles of the outcome, whereas for children with non-CP MD, decreases were not significant at quantile 90 and more pronounced at the lower HRQoL quantiles. The last point suggests that there may be mitigating or protective factors that preserve HRQoL for some children and calls for future studies focusing on identifying protective individual, familial or broader environmental factors. Differences persisted after exclusion of children with moderate to severe NDI and among children not receiving any MRHC services over the past year, illustrating a concrete detrimental impact in their activities of daily living and calling for continued follow-up of children born EPT beyond two years and for better diagnosis and health service provision for children with non-CP MD.

8.2. Strengths and limitations of this doctoral work

This section summarizes the main strengths and limitations of this doctoral work related to the study population and its composition, the temporality, as well as the measurement tools. For the principal limits, we propose approaches for overcoming them in future studies.

8.2.1. The study population

Large population-based sample from a multi-country cohort

A strength of this doctoral research is its use of a large, population-based sample including more than 800 EPT children. Other studies on this topic do not focus specifically on children born before 28 weeks' GA or have much smaller samples of between 50 and 300 children (Evensen et al., 2020; van Hoorn et al., 2021; Linsell et al., 2016; Vieira and Linhares, 2016; Williams et al., 2010; Zwicker and Harris, 2008). Furthermore, in addition to

being a population-based sample, our analyses are based on children from 19 European regions, making the results generalisable to most of the European continent and several high-income countries. Rogers and Hintz (2016), in a review discussing research on the early neurodevelopmental outcomes of EPT infants, highlight the struggle for study conclusions to be generalisable with “many of the hundreds of articles on the topic [that] are small, single-centre observational studies” and “relatively few report data from large, prospective, population-based cohorts.” Due to the small sample sizes in some countries, however, we were unable to explore country differences. While loss to follow-up was a limitation of this work, we were able to correct for attrition bias with IPW techniques using baseline data on the full cohort. But we cannot exclude some bias linked to unobserved characteristics affecting loss to follow-up.

A restricted gestational age group

Although children with a gestational age <32 weeks were included in the EPICE-SHIPS study, only the sub-group of children born EPT, who are the most at risk of poor outcomes, had a clinical assessment to evaluate neurocognitive and motor functioning at five years of age because of funding and logistic constraints. For this reason, our study population was limited to these children and we were unable to analyse data on children between 28 and 31 weeks of GA. However, GA is a continuous exposure and other research has shown that the prevalence of MD at these GA is also higher when compared to children at term (Evensen et al., 2020; Williams et al., 2010). The French EPIPAGE-2 study (Ancel et al., 2014), which has the same data items as the EPICE-SHIPS project (three of the EPICE-SHIPS regions were in EPIPAGE-2), but carried out motor assessment for all VPT children, could be a resource for assessing whether our results on risk factors, healthcare service use and HRQoL can be extrapolated to children with higher GA.

The absence of a control group is also a limit and made it impossible to compare outcomes between children born EPT and contemporaneous term-born controls. Although this was not an objective of this research, a control group would have made it possible to assess the published norms of the MABC-2 in a term population. While studies with controls report good calibration of MABC-2 norms in their control samples (Evensen et al., 2020), having control groups would have been valuable for our study given the wide differences in study norms between countries and the absence of local norms in all countries, leading to the decision to use the United Kingdom norms for all countries (Costa et al., 2020). This question

could also be explored further, in part, using the French EPIPAGE-2 study, which uses a subset of the French national cohort of children (the ELFE study) who were also assessed using the MABC-2 as a control population (Ancel et al., 2014; Charles et al., 2020). With a control group we would also have been able to explore the potential specific impact of extreme prematurity on HRQoL, despite the developmental comorbidities.

8.2.2. Temporality

Assessing children at around five years of age is a strength of this study for at least two reasons. First, at this age, information on CP and non-CP MD are considered to be reliable. The GMFCS classification system is unstable in the first years of life, especially for ambulant CP. A confirmation of the CP diagnosis after four years of age is recommended to minimise false diagnoses and include those with milder symptomatology (Hafström et al., 2018; Smithers-Sheedy et al., 2014; Surveillance of Cerebral Palsy in Europe, 2000). Similarly, for non-CP MD, four to five years of age appears to be the minimum required to properly distinguish between normal developmental trajectories, slow motor development and abnormal development (Ferrari et al., 2012; McIntyre et al., 2011), taking into consideration the “catch-up” that some children can have in their early years and the reliability of tools assessing motor skills (Blank et al., 2019; Spittle and Orton, 2014). In addition, developmental motor problems may sometimes appear or become visible only at early school-age with the increasing difficulty of motor tasks (Doyle et al., 2014). For instance, fine motor skills or manual dexterity are required for writing, drawing or manipulating objects (Evensen et al., 2020). Secondly, the first six years of life is considered as a critical period of motor development with the reorganization of the neural connections required for the acquisition of most motor skills in the postnatal period (Chakrabarty and Martin, 2010; Ferrari et al., 2012). Thus, when developmental motor problems are detected at this age, it is still possible to take advantage of the greater neuroplasticity of the developing brain and its ability to reorganise neural connectivity in response to new experiences or training (Chorna et al., 2020), and thus propose more effective interventions.

However, an important limitation related to temporality and our observational design is the measurement of some risk factors at the same time as our study outcomes, namely maternal education level and household unemployment status and similarly, the concurrent assessment of developmental motor problems, health service use and HRQoL. This limits our ability to interpret causality since the outcomes may affect the risk factors (for instance,

parental employment being affected by severe impairments of the child). However, as relates to the HRQoL, reverse causality seems unlikely. For the analysis of MRHC service use among children with developmental motor problems, it is also difficult to speculate on causality.

8.2.3. The measurement tools

The Movement Assessment Battery for Children – 2nd Edition

As discussed in the individual studies, the MABC-2 is a commonly used and validated measure of non-CP MD (Blank et al., 2012; Henderson et al., 2007; de Kieviet et al., 2009), even in a high-risk population of EPT children (Dewey et al., 2011) and constitutes a strength of our research work. MABC-2 national norms do not exist in all countries and the choice of norms have been shown to potentially affect the classification of MD (Costa et al., 2020). We therefore used the MABC-2 United Kingdom norms, originally developed for the test and most commonly used in the published literature (Costa et al., 2020; Henderson et al., 2007). This allowed us to derive percentile scores for all children and harmonise results between countries. In addition, we carried out sensitivity analyses to confirm that risk factor results were robust to use of national norms. Although we had procedures to standardise reporting of the MABC-2 test, examiner reliabilities across sites were not assessed. However, the MABC-2 is considered to have a good to excellent inter-rater reliability and test-retest reliability (Blank et al., 2019).

Cerebral palsy diagnosis

Even though we had information on CP for almost all children at five years of age (only three them out of the 1,021 followed were excluded because of missing information), the collection of this data using parental report questionnaire is a limit of our research. Parent-reported information is prone to recall bias or misunderstanding of the diagnosis and this may have led to misclassifying some children even if parents were asked to report a diagnosis of CP given by a doctor or another health professional.

Another important limit of our research is the absence of information concerning CP types and grades of severity which may affect the type and magnitude of risk factors, MRHC support and consequences for day-to day life. For instance, almost all children with unilateral CP can walk compared to approximately half of those with bilateral CP (Cheong et al., 2020; Galea et al., 2019) with direct impact on daily activities. As illustrated by Rosenbaum et

al. (2002), motor functions are incrementally reduced from CP with GMFCS level I to GMFCS level V. Again, the French EPIPAGE-2 study (Ancel et al., 2014), close to the EPICE-SHIPS cohort, has a CP diagnosis both reported by a medical doctor directly and classified using the GMFCS levels. Thus, it would be interesting to use these data to overcome the limits just described. In EPICE-SHIPS, we also have parent reported appreciations of their child's motor function, including walking ability, that we could use to approximate the severity of CP in future work, even though this is not a validated approach.

Lastly, we cannot exclude some misclassification error between the group significant MD and CP, with some children who have undetected CP. However, as presented previously, at five years of age, most children will have a valid and stable diagnosis of CP (Hafström et al., 2018; Smithers-Sheedy et al., 2014; Surveillance of Cerebral Palsy in Europe, 2000).

Questions on use of health services

For the measurement of healthcare service use, we relied on a parental questionnaire, but recall bias might have affected the accuracy of the answers. Previous studies have shown that recall accuracy varies depending on the type of health service and the patient population (Leggett et al., 2016; Seppänen et al., 2022b). For instance, general practitioner visits have been found to be both under and over-reported, whereas other services, such as physiotherapy visits, tend to be over-reported. To limit bias, a standardised and harmonised data collection was used and health care provider proposals were adapted from previous results in this cohort during the follow-up at two years of age and verified by researchers in each country (Seppänen et al., 2019). The objective was to fully reflect local care practices relevant to the age group, and parents could also report additional services used as free-text responses.

Other important limits are the lack of information on the purpose of the health care received and whether care was for prevention or treatment. There was also limited details about the frequency of visits, with parents reporting only the number of health care visits over the past year. It was impossible to consider the appropriateness of the care and thus determine whether non-use is provider or user-related. Indeed, the non-use of MRHC services may also be due to a lack of health care professional availability, difficulties experienced in attending appointments (e.g., in time or resources), etc.

The Pediatric Quality of Life Inventory™

The PedsQL generic core scale is a tool which has demonstrated a good validity and reliability in healthy school populations, and in paediatric populations with acute or chronic health conditions (Varni et al., 2006, 2003, 2001). In addition, because EPT children may be affected in several ways, a generic instrument (i.e., designed to assess HRQoL in the general population), as opposed to condition-specific instruments (i.e., designed to assess HRQoL in individuals with a specific disease or impairment), seems to be the most appropriate tool to assess HRQoL in this population (Saigal, 2013; Vieira and Linhares, 2016). However, the CP module which could have been relevant for those children (Varni et al., 2006), was not included.

Due to the young age of children and the severity of their impairments for some of them (Eiser and Morse, 2001b; Mottram and Holt, 2010; Saigal and Tyson, 2008; Vederhus et al., 2010; Vieira and Linhares, 2016; Waters et al., 2009), we used the parental version of the PedsQL, with parents answering on behalf of the child. Potential differences between self- and parental report of the child's HRQoL have been described in the literature (Eiser and Morse, 2001b; Jardine et al., 2014; Karras et al., 2019; Upton et al., 2008; Zwicker and Harris, 2008), although they are not systematic (Gire et al., 2019; Stokes et al., 2017; Upton et al., 2008), and may vary depending on the domains that are being measured (Saigal and Tyson, 2008; Upton et al., 2008): with relatively good agreement found between parent and child on the more observable items, such as physical activity and functioning (Eiser and Morse, 2001b; Saigal and Tyson, 2008; Upton et al., 2008; Vieira and Linhares, 2016).

These differences do not indicate a "right" or "wrong" answer, but are rather a consequence of each individual's beliefs about the child's health and well-being (Upton et al., 2008). However, contrary to quality of life measures which refer to a child's feelings and judgements about his or her life, HRQoL assesses a child's functional status (Davis et al., 2006; Vederhus et al., 2010), i.e., "the child's ability to perform daily activities that are essential to meet his or her basic needs, fulfil roles, and maintain health and well-being" (Drotar, 2004, p358). By conception, the PedsQL has a strong focus on the measurement of functional aspects of the HRQoL (Ravens-Sieberer et al., 2006), with the majority of items (18 out of 23) concerning what children can do rather than how they feel (Upton et al., 2008; Waters et al., 2009). For all these reasons, proxy respondents can provide valuable information and make it possible to include children who are unable to self-report as they are also the most impaired (Hack et al., 2011; Saigal and Tyson, 2008). In this context, parents are probably best placed

to report the difficulties encountered by their child (Saigal et al., 1999). However, key limits persist, as encapsulated by Saigal and Tyson (2008, p62) in this statement, “ironically, it is not possible to obtain the personal perspectives where these are most need, i.e., from those who are too young, sick, disabled, or cognitively impaired to respond themselves.”

8.3. Interpretation and contribution to the evidence-base

This research contributed new knowledge on developmental motor problems experienced by children after EPT birth. First, our estimate of MD among non-CP children in this large European sample makes it clear that MD is highly prevalent in EPT populations. This has been an outstanding question given the large discrepancies in estimated prevalence rates between studies, with variation from around 10% to more than 40% (Bolk et al., 2018; Bos et al., 2013; Evensen et al., 2020; Setänen et al., 2016; Spittle et al., 2021; Williams et al., 2010). We also found differences between countries after adjusting for population case-mix, which suggest that some context-specific factors may explain some of the variation in previous studies. Nonetheless, prevalence of MD was high in all participating countries. Our observed CP rate of 10% is consistent with the contemporaneous literature on children born EPT (Himpens et al., 2008; Oskoui et al., 2013; Pascal et al., 2018), adding credence to our findings of high MD among children without CP. In sum, our studies suggest that about 60% of children born EPT face developmental motor problems, highlighting this major global health concern.

We also found that these developmental motor problems were associated with worse child HRQoL, with the lowest level for children with CP, followed by those with significant MD and at risk of MD, in comparison to EPT children without MD. Differences persisted after exclusion of children with other developmental comorbidities and among children not receiving any MRHC services over the past year. In this context, our results have practice and policy implications that relate to i) perinatal care and prevention, ii) the social and familial environment, iii) follow-up and care of children born EPT, and iv) societal-level interventions that could limit the detrimental consequences of developmental motor problems on day-to-day life.

8.3.1. Implications for perinatal care and prevention policies

Our results on perinatal and neonatal risk factors associated with CP and non-CP MD provide information which may help healthcare professionals identify specific subgroups at

risk of developmental motor problems and target interventions. Looking at the risk profiles for CP and non-CP MD, it seems that the risk of CP is associated with risk factors that have been shown to be modifiable with perinatal interventions and quality initiatives in the neonatal unit (Zeitlin et al., 2010), e.g., IVH, oxygen support, Apgar, or delivery in care unit level 3. These interventions, implemented in many centres over past decades may contribute to explaining the decreasing trend in CP among children born EPT (Platt et al., 2007; Reid et al., 2016). For instance, Rizzolo et al. (2020) analysed four evidence-based practices on infants born <29 weeks' GA admitted to neonatal intensive care units, i.e., antenatal corticosteroids, antenatal magnesium sulphate for neuroprotection, deferred cord clamping and maintenance of normothermia on admission; and found that infants exposed to at least two evidence-based practices had lower odds of death and/or severe neurological injury than those exposed to no evidence-based practices. Implementing a neuroprotection care bundle, i.e., a combination of neuroprotection interventions and protocolisation of hemodynamic and respiratory managements, on infants born <29 weeks' GA in a Canadian neonatal intensive care unit, Murthy et al. (2020) observed a reduction in death and severe brain injury; confirming the short-term benefits. Benlamri et al. (2022), using the same participants but with an additional neonatal follow-up at 18-24 months adjusted age, highlighted also the long-term benefits with an observed reduction in severe NDI and any Bayley Scales of Infant and Toddler Development – 3rd Edition motor, language, or cognitive composite score >2 SD. However, results specifically on the prevention of CP were non-significant. In contrast, non-CP MD are linked to risk factors for which interventions are less effective, i.e., low GA, SGA or sociodemographic factors. There are few medical interventions to prevent preterm birth or fetal growth restriction, mainly restricted to groups of high-risk patients with previous obstetric history of these complications (Delnord and Zeitlin, 2019). However, these interventions have shown limited potential for reducing overall preterm birth rates (Chang et al., 2013). Broader population-level preventive strategies may also be effective, such as those promoting smoking cessation and healthy weight gain or policies to reduce exposure to air pollution (Delnord and Zeitlin, 2019). Our results showing high prevalence of motor complications and their consequences for children add incentives to focus on population prevention. Reducing the preterm birth rate is an important focus for decreasing the prevalence of developmental motor problems (Iams et al., 2008).

8.3.2. Support the social and familial environment and involve parents

We found many sociodemographic factors associated with non-CP MD, with unemployment status associated with both being at risk for MD and having significant MD, and young maternal age, low maternal educational level and maternal birth outside of Europe associated with significant MD. These results illustrate the importance of considering social circumstances in public health programmes which target children born EPT. In addition, understanding how social factors interact with medical and biological risk is an important area for future research in order to more accurately identify at-risk groups and understand risk and resilience mechanisms. In an article entitled “Can the home environment promote resilience for children born very preterm in the context of social and medical risk?”, Treyvaud et al. (2012) used a parent-reported questionnaire to estimate the optimality of the home environments among 166 children born <30 weeks’ GA. This tool measures home environments that are more likely to support optimal child development, by asking several aspects of the home environment, e.g., parental involvement, provision of appropriate play materials, etc. A more optimal home environment was predictive of improved outcomes for children at two years corrected age, supporting the potential of the home environment as a target for intervention for VPT children. However, results were non-significant for motor development. The authors explain this by the fact that motor development may be more strongly linked to biological risk factors among preterm children which would be less affected by family context (Laucht et al., 1997). However, Laucht et al. (1997), in analyses of developmental outcome (including motor, cognitive and socio-emotional functioning) of 350 infants at 3, 24 and 54 months, found that psychosocial risks become more prominent determinants of outcome with age, while biological risks decrease in influence. Differences in the age of assessment could explain why the home environment has been associated with motor development in term-born school-age children (Ferreira et al., 2018). Our research also confirms an association with social risk at 5 years of age.

In our research, we distinguished between children at risk for MD and with significant MD. These children are usually combined together with children with significant MD or included in the category of children without MD (Evensen et al., 2020). Even if some factors were associated with significant MD only, many others – including household unemployment status for the sociodemographic factors – were also associated with being at risk for MD. These minor difficulties, less often examined, also have concrete detrimental consequences in daily activities (as shown in the last chapter). Our results show the utility of making this

distinction and of undertaking research on the link between mild developmental motor problems and the social context.

Other studies have shown that parent-guided interventions, i.e., involving parents in the intervention which is still monitored by a professional, were more effective than programmes focused on the child or the parent alone to improve motor performance in children with non-CP motor problems (Rogers and Hintz, 2016; Smits-Engelsman et al., 2013; van Wassenaeer-Leemhuis et al., 2016). The involvement of parents ensures that the learned skills will continue to be used after the formal intervention. In the Netherlands, the encouraging results of the Infant Behavioral Assessment and Intervention Program at different ages (Koldewijn et al., 2005; Van Hus et al., 2013; Verkerk et al., 2011), led to the nationwide implementation of a postdischarge responsive parenting intervention program for VPT children, the TOP program (Transmural developmental support for VPT infants and their parents), which is now part of routine care (Jeukens-Visser et al., 2021).

8.3.3. Follow-up of children born extremely preterm

Children born EPT are an identifiable high-risk group for whom structured and specialised follow-up programmes are warranted (Doyle et al., 2014). In the EPICE-SHIPS cohort, 90.3% of all VPT children had used follow-up services at some point after discharge, but only 27.3% were still followed at five years of age, with wide variation between countries (from 10.9% to 58.4%) (Seppänen et al., 2022a). In our study, we found that only 42.8% of EPT children with significant MD and 25.9% of children who were at risk for MD were receiving MRHC services at five years of age, despite the HRQoL reduction we observed among them. Furthermore, the follow-up rates varied greatly between the countries, from 23.3% to 66.7% for children with significant MD and from 4.5% to 33.3% for children at risk for MD. In contrast, and reassuringly, almost 90% of children with a CP diagnosis were receiving MRHC services with similar rates in all the countries. These results, and the potential effectiveness of various interventions to improve motor function in children with CP and non-CP MD (Booth et al., 2018; Dewar et al., 2015; Smits-Engelsman et al., 2013), are in favour of guidelines to follow-up and support of children with non-CP motor problems during at least their first five years of life. International guidelines exist for healthcare provision for children with a CP diagnosis (Agency for Clinical Innovation, 2018; Morgan et al., 2021; National Institute for Health and Care Excellence, 2017b, 2017a), but recommendations are much more variable for EPT children without a formal diagnosis of impairment. For instance, in the last French National

guidelines (Haute Autorité de Santé, 2020), six assessments are recommended up to five years of age for all VPT children. In the United Kingdom (National Institute for Health and Care Excellence, 2017a), three assessments up to two years of corrected age are recommended, as well as an additional developmental assessment at four years of age for EPT children only. However, recent international and national guidelines have been developed recently (European Foundation for the Care of Newborn Infants, 2018; Orton et al., 2018) which may promote greater standardisation of policy in European countries.

In addition to the evaluation of motor development, guidelines for the follow-up of children born very preterm highlight the importance of multidisciplinary teams in developmental surveillance (National Institute for Health and Care Excellence, 2017b, 2017a). Multiple developmental impairments are frequent after EPT birth (Moreira et al., 2014; Twilhaar et al., 2021). For instance, Van Hus et al. (2014) assessed developmental deficits in five-year-old children born <30 weeks' GA and found that 32% had motor problems. Among these children, many also had other developmental deficits, namely, 58% had complex minor neurological dysfunctions, 54% had a low intelligence quotient, 69% had a slow processing speed, 58% had visuomotor coordination problems, and 27%, 50%, and 46% had conduct, emotional, and hyperactivity problems, respectively. Additional findings suggesting that children with DCD could also benefit from therapeutic support addressing psychosocial and emotional challenges that arise from the condition (Li et al., 2018).

Training of health care professionals to detect developmental motor problems among children born EPT could lead to improvements in detection and management of these difficulties (Camden et al., 2015; Harris et al., 2015). In our study on healthcare service use, we found that children with other developmental difficulties were more likely to receive MRHC services. This may suggest health care professionals are less familiar with non-CP MD than other developmental difficulties (Blank et al., 2019; Wilson et al., 2013). For instance, in an online survey of almost 600 physicians from Canada, the United States of America and the United Kingdom, >80% were somewhat or very familiar with ADHD, learning disability and obsessive-compulsive disorder. However, only 41% of paediatricians and 23% of general practitioners had knowledge of DCD, with only around half of them having ever diagnosed it. Thus, non-CP MD may be underrecognized by health care professionals which results in affected children receiving limited assistance to face their challenges (Dewey et al., 2011). In one study from the EPICE-SHIPS cohort measuring parents' perceptions of post-discharge

health care for their children which based on over 1,000 unique free-text responses, Seppänen et al. (2021) highlighted the recurrence of comments on the lack of knowledge on the consequences of preterm birth among generalists practitioners and nurses.

8.3.4. Beyond health care: schooling, social integration and the broader context

Research to follow-up children beyond early childhood is important for understanding the full consequences of developmental motor problems. In particular, it has been shown that MD on their own and in combination with other developmental comorbidities, have been associated with lower educational achievement (Moreira et al., 2014). Burns et al. (2004), for instance, concluded that the severity of minor neurological, motor and coordination problems are one of the major predictors of school failure. VPT children with educational problems at five years of age have been found to have more neurodevelopmental disorders than VPT children without educational problems (van Kessel-Feddema et al., 2007); and persistence of motor difficulties from early school-age to adolescence was associated with worse academic achievement in adolescence among children born EPT (Costa et al., 2017).

Focus on the school environment is also important because motor problems may become visible only at school-age, with the increasing of the difficulty of motor tasks (Doyle et al., 2014). For instance, fine motor skills or manual dexterity are required for writing, typing, drawing or manipulating objects (Evensen et al., 2020). For this reason, educating teachers about the movement consequences of VPT birth, as done in this series of videos focusing on cognitive skills and developed by the PRISM Study team supervised by the Professor Samantha Johnson (<https://www.nottingham.ac.uk/helm/dev/prism/index.html>), for example, could contribute to improving the understanding and management of MD in school. More generally, research on the education of children after VPT birth emerged as the highest ranking theme in a recent consensus process with experts about priority research themes on the consequences of VPT birth (Zeitlin et al., 2020b).

Resiliency mechanisms and support for inclusion and healthy physical activity

Quantile regression models, used to look at the daily consequences of developmental motor problems, showed that some EPT children with non-CP MD had very similar HRQoL as children without MD. This suggests that there may be mitigating or protective factors that preserve HRQoL for some children. For instance, there resiliency mechanisms that allow children to have good day-to-day functioning and to be satisfied with their lives and what they

are able to achieve despite their disabilities. Known as the disability paradox, this is directly related to society's tendency to view disability as a continuing tragedy (Albrecht and Devlieger, 1999). In their study including 153 persons with disabilities interviewed, Albrecht and Devlieger (1999) found that over half of the individuals living with serious disabilities, limited incomes and benefits, serious limitations in daily activities and who were relatively socially isolated, reported a good or excellent quality of life. Assessing the QoL of 8-12-year-old children with CP, Dickinson et al. (2007) found that children able to self-report, i.e., with the less severe CP (39% of the sample had a severe intellectual impairment and could not self-report), had similar QoL than other children in most domains. This ability of individuals to have a good QoL even in the presence of risk factors is part of the resiliency definition (Masten et al., 2021). Thus, a handicap, defined by the WHO (World Health Organization, 1980), as "a disadvantage for a given individual that limits or prevents the fulfilment of a role that is normal," is also directly related to the organisation of the society in term of human and material possibilities and the place made to enable all individuals having a fulfil and autonomous life. Although it is important to continue to develop research on the prevention and treatment of developmental motor problems among EPT children, these resiliency mechanisms, as well as the society's view of these difficulties are important strategies for reducing the detrimental consequences of motor problems.

Another research area focuses on the cultural and societal expectations regarding the motor development of these children. As highlighted by Blank et al. (2019, p256), "a child from a culture, which limits physical activity or which provides little opportunity for motor learning may present like a child with DCD (at least partially)." In our research, differences in non-CP MD rates persisted between countries even after adjustment on sociodemographic and clinical factors. Coupled with results showing the impact of the choice of MABC-2 norms on prevalence estimates at the country-level (Costa et al., 2020), this raises questions about contextual factors which could affect motor outcomes among EPT children. For instance, preschool, school, or public health programmes which differ between European countries (Daugbjerg et al., 2009; European Union, 2008; World Health Organization, 2015) and may influence the global motor development and therefore affect performance on MABC-2 tests (Cheung et al., 2019; Hills et al., 2015; Yuksel et al., 2020). Because the sample sizes per country were limited and must be interpreted with caution, we were unable to explore these questions further in our study. However, further research investigating cross-country differences in non-CP MD are needed and could inform prevention efforts.

Chapter 9 – Conclusions and perspectives

After EPT birth, over half of children face developmental motor problems during childhood. The multiple clinical and sociodemographic risk factors associated with CP and non-CP MD provide insight for strategies and further research to improve medical practices, as well as support for families and ultimately to reduce the prevalence of these motor problems. Our results can also be useful for identifying at-risk children for whom additional health monitoring may be necessary to improve detection and intervention for developmental difficulties. Apart from those with CP, the majority of children with non-CP MD were not receiving MRHC services. This raises questions about current healthcare provision to children born EPT and whether this absence of health care constitutes a potential loss of opportunity for early interventions. The fact that these developmental motor problems, even for children categorised as being at risk for MD and those without other developmental difficulties, affect HRQoL highlights the importance of recognising the public health relevance of these difficulties and providing support for children and their families.

In addition, to the specific questions for research raised in *section 8.3*, there are several areas of future research that follow on the work presented in this doctoral work. A first area is the exploration of brain abnormalities and neurodevelopmental pathways, e.g., using MRI techniques, in children with non-CP MD (Kelly et al., 2015; Spittle et al., 2011). This research could improve understanding of the potential continuum between CP and non-CP MD posited by some researchers (Pearsall-Jones et al., 2010), with complex minor neurological dysfunction regarded as a borderline form of CP (Ferrari et al., 2012). In this doctoral research, we observed similarities in some risk factors for non-CP MD and CP, but risk factor profiles remained different and probably indicative of distinct aetiologies. However, we found severe IVH (grades III and IV) and cPVL also associated with non-CP MD, even if it was at a much lower order of magnitude than it is the case for CP. This exploration of brain function could also provide information on the mechanisms leading to the motor problems which may be different depending on the motor domain. For instance, in Study 1, as well as in the literature (Evensen et al., 2020; de Kieviet et al., 2009), the classification of non-CP MD may differ depending on the motor domain assessed, and a remaining question of this doctoral work is whether results would be different, with respect to the risk factors, MRHC support and daily consequences, if each motor domain were analysed individually.

Another research area relates to the use of parent report for the detection of motor difficulties. Currently, motor function assessments are expensive, time consuming and require

professionals with expertise (Dewey et al., 2011). Having a validated parent-report instrument for movement difficulties could facilitate rapid screening and be integrated into children's routine health visits. In a study carried out on the EPICE-SHIPS cohort during this doctoral work, we assessed the predictive validity of parent-reported gross motor impairment at two years of age to detect significant MD at five years of age, using the MABC-2. Results showed a high specificity and positive predictive value, but a low sensitivity (Costa et al., 2023).

Finally, research on the long-term consequences of these developmental motor problems in terms of cardiometabolic health is a further area of development. Current research in the general population have shown an association between motor problems and poorer cardiorespiratory fitness, reduced physical activity and obesity (Cairney et al., 2007; Faught et al., 2005). In this context, the place of physical activity, also directly associated with cardiorespiratory fitness and obesity, could play the role of mediator to mitigate the detrimental effects of motor problems on cardiometabolic health (Faught et al., 2005). Research for effective interventions, as well as global politic strategies, to improve the physical activity level of children with motor problems, no matter if they are born EPT or at term, is a potential key tool to both improve the physical abilities of the children (e.g., aerobic capacity, leg power, grip strength, etc.), directly related to the physical independence, healthy weight and their cardiometabolic health (World Health Organization, 2015).

References

- Adams-Chapman I, Heyne RJ, DeMauro SB, Duncan AF, Hintz SR, Pappas A, et al. Neurodevelopmental Impairment Among Extremely Preterm Infants in the Neonatal Research Network. *Pediatrics* 2018;141:e20173091. <https://doi.org/10.1542/peds.2017-3091>.
- Agency for Clinical Innovation. Management Of Cerebral Palsy In Children: A Guide For Allied Health Professionals. 2018.
- Albrecht GL, Devlieger PJ. The disability paradox: high quality of life against all odds. *Soc Sci Med* 1999;48:977–88. [https://doi.org/10.1016/s0277-9536\(98\)00411-0](https://doi.org/10.1016/s0277-9536(98)00411-0).
- Allotey J, Zamora J, Cheong-See F, Kalidindi M, Arroyo-Manzano D, Asztalos E, et al. Cognitive, motor, behavioural and academic performances of children born preterm: a meta-analysis and systematic review involving 64 061 children. *BJOG Int J Obstet Gynaecol* 2018;125:16–25. <https://doi.org/10.1111/1471-0528.14832>.
- American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine. Obstetric Care consensus No. 6: Periviable Birth. *Obstet Gynecol* 2017;130:e187–99. <https://doi.org/10.1097/AOG.0000000000002352>.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Fifth Edition. Arlington, VA: 2013.
- Ancel P-Y, Goffinet F, EPIPAGE 2 Writing Group. EPIPAGE 2: a preterm birth cohort in France in 2011. *BMC Pediatr* 2014;14:97. <https://doi.org/10.1186/1471-2431-14-97>.
- Ancel P-Y, Goffinet F, EPIPAGE-2 Writing Group. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. *JAMA Pediatr* 2015;169:230–8. <https://doi.org/10.1001/jamapediatrics.2014.3351>.
- Anderson PJ. Neuropsychological outcomes of children born very preterm. *Semin Fetal Neonatal Med* 2014;19:90–6. <https://doi.org/10.1016/j.siny.2013.11.012>.
- Arnaud C, White-Koning M, Michelsen SI, Parkes J, Parkinson K, Thyen U, et al. Parent-reported quality of life of children with cerebral palsy in Europe. *Pediatrics* 2008;121:54–64. <https://doi.org/10.1542/peds.2007-0854>.
- Atkinson J, Braddick O. Visual and visuocognitive development in children born very prematurely. *Prog Brain Res* 2007;164:123–49. [https://doi.org/10.1016/S0079-6123\(07\)64007-2](https://doi.org/10.1016/S0079-6123(07)64007-2).
- Aubert AM, Costa R, Ådén U, Cuttini M, Männamaa M, Pierrat V, et al. Movement Difficulties at Age Five Among Extremely Preterm Infants. *Pediatrics* 2022:e2021054920. <https://doi.org/10.1542/peds.2021-054920>.
- Aubert AM, Costa R, Johnson S, Ådén U, Cuttini M, Koopman-Esseboom C, et al. Risk factors for cerebral palsy and movement difficulties in 5-year-old children born extremely preterm. *Pediatr Res* 2023. <https://doi.org/10.1038/s41390-022-02437-6>.
- Audigier V, White I, Jolani S, Debray T, Quartagno M, Carpenter J, et al. Multiple Imputation for Multilevel Data with Continuous and Binary Variables. *Stat Sci* 2018;33:160–83. <https://doi.org/10.1214/18-STS646>.

- Austin PC, Escobar M, Kopec JA. The use of the Tobit model for analyzing measures of health status. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil* 2000;9:901–10. <https://doi.org/10.1023/a:1008938326604>.
- Baron IS, Rey-Casserly C. Extremely preterm birth outcome: a review of four decades of cognitive research. *Neuropsychol Rev* 2010;20:430–52. <https://doi.org/10.1007/s11065-010-9132-z>.
- Beaino G, Khoshnood B, Kaminski M, Pierrat V, Marret S, Matis J, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev Med Child Neurol* 2010;52:e119-125. <https://doi.org/10.1111/j.1469-8749.2010.03612.x>.
- Benlamri A, Murthy P, Zein H, Thomas S, Scott JN, Abou Mehrem A, et al. Neuroprotection care bundle implementation is associated with improved long-term neurodevelopmental outcomes in extremely premature infants. *J Perinatol Off J Calif Perinat Assoc* 2022;42:1380–4. <https://doi.org/10.1038/s41372-022-01443-0>.
- Berbis J, Einaudi MA, Simeoni MC, Brévaut-Malaty V, Auquier P, d’Ercole C, et al. Quality of life of early school-age French children born preterm: a cohort study. *Eur J Obstet Gynecol Reprod Biol* 2012;162:38–44. <https://doi.org/10.1016/j.ejogrb.2012.02.006>.
- Biancotto M, Borean M, Bravar L, Pelamatti GM, Zoia S. *Movement Assessment Battery for Children-2, Italian Adaptation*, 2nd ed. Giunti O.S. Prato, Italy: 2013.
- Blank R, Barnett AL, Cairney J, Green D, Kirby A, Polatajko H, et al. International clinical practice recommendations on the definition, diagnosis, assessment, intervention, and psychosocial aspects of developmental coordination disorder. *Dev Med Child Neurol* 2019;61:242–85. <https://doi.org/10.1111/dmcn.14132>.
- Blank R, Smits-Engelsman B, Polatajko H, Wilson P, European Academy for Childhood Disability. European Academy for Childhood Disability (EACD): recommendations on the definition, diagnosis and intervention of developmental coordination disorder (long version). *Dev Med Child Neurol* 2012;54:54–93. <https://doi.org/10.1111/j.1469-8749.2011.04171.x>.
- Blauw-Hospers CH, Hadders-Algra M. A systematic review of the effects of early intervention on motor development. *Dev Med Child Neurol* 2005;47:421–32. <https://doi.org/10.1017/s0012162205000824>.
- Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller A-B, et al. Born too soon: the global epidemiology of 15 million preterm births. *Reprod Health* 2013;10 Suppl 1:S2. <https://doi.org/10.1186/1742-4755-10-S1-S2>.
- Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet Lond Engl* 2012;379:2162–72. [https://doi.org/10.1016/S0140-6736\(12\)60820-4](https://doi.org/10.1016/S0140-6736(12)60820-4).
- Boardman JP, Craven C, Valappil S, Counsell SJ, Dyet LE, Rueckert D, et al. A common neonatal image phenotype predicts adverse neurodevelopmental outcome in children born preterm. *NeuroImage* 2010;52:409–14. <https://doi.org/10.1016/j.neuroimage.2010.04.261>.

- Bolisetty S, Dhawan A, Abdel-Latif M, Bajuk B, Stack J, Lui K, et al. Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. *Pediatrics* 2014;133:55–62. <https://doi.org/10.1542/peds.2013-0372>.
- 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;172:765–74. <https://doi.org/10.1001/jamapediatrics.2018.1394>.
- Booth ATC, Buizer AI, Meyns P, Oude Lansink ILB, Steenbrink F, van der Krogt MM. The efficacy of functional gait training in children and young adults with cerebral palsy: a systematic review and meta-analysis. *Dev Med Child Neurol* 2018;60:866–83. <https://doi.org/10.1111/dmcn.13708>.
- Bos AF, Van Braeckel KNJA, Hitzert MM, Tanis JC, Roze E. Development of fine motor skills in preterm infants. *Dev Med Child Neurol* 2013;55 Suppl 4:1–4. <https://doi.org/10.1111/dmcn.12297>.
- Bracewell M, Marlow N. Patterns of motor disability in very preterm children. *Ment Retard Dev Disabil Res Rev* 2002;8:241–8. <https://doi.org/10.1002/mrdd.10049>.
- Burns Y, O’Callaghan M, McDonnell B, Rogers Y. Movement and motor development in ELBW infants at 1 year is related to cognitive and motor abilities at 4 years. *Early Hum Dev* 2004;80:19–29. <https://doi.org/10.1016/j.earlhumdev.2004.05.003>.
- Cade BS, Noon BR. A gentle introduction to quantile regression for ecologists. *Front Ecol Environ* 2003;1:412–20. [https://doi.org/10.1890/1540-9295\(2003\)001\[0412:AGITQR\]2.0.CO;2](https://doi.org/10.1890/1540-9295(2003)001[0412:AGITQR]2.0.CO;2).
- Cairney J, Hay JA, Faught BE, Flouris A, Klentrou P. Developmental coordination disorder and cardiorespiratory fitness in children. *Pediatr Exerc Sci* 2007;19:20–8. <https://doi.org/10.1123/pes.19.1.20>.
- Camden C, Wilson B, Kirby A, Sugden D, Missiuna C. Best practice principles for management of children with developmental coordination disorder (DCD): results of a scoping review. *Child Care Health Dev* 2015;41:147–59. <https://doi.org/10.1111/cch.12128>.
- Chakrabarty S, Martin JH. Postnatal Development of a Segmental Switch Enables Corticospinal Tract Transmission to Spinal Forelimb Motor Circuits. *J Neurosci* 2010;30:2277–88. <https://doi.org/10.1523/JNEUROSCI.5286-09.2010>.
- Chang HH, Larson J, Blencowe H, Spong CY, Howson CP, Cairns-Smith S, et al. Preventing preterm births: analysis of trends and potential reductions with interventions in 39 countries with very high human development index. *Lancet Lond Engl* 2013;381:223–34. [https://doi.org/10.1016/S0140-6736\(12\)61856-X](https://doi.org/10.1016/S0140-6736(12)61856-X).
- Charles MA, Thierry X, Lanoe J-L, Bois C, Dufourg M-N, Popa R, et al. Cohort Profile: The French national cohort of children (ELFE): birth to 5 years. *Int J Epidemiol* 2020;49:368–369j. <https://doi.org/10.1093/ije/dyz227>.
- Chawanpaiboon S, Vogel JP, Moller A-B, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health* 2019;7:e37–46. [https://doi.org/10.1016/S2214-109X\(18\)30451-0](https://doi.org/10.1016/S2214-109X(18)30451-0).

- Chen J, Smith LEH. Retinopathy of prematurity. *Angiogenesis* 2007;10:133–40. <https://doi.org/10.1007/s10456-007-9066-0>.
- Cheong JL, Olsen JE, Lee KJ, Spittle AJ, Opie GF, Clark M, et al. Temporal Trends in Neurodevelopmental Outcomes to 2 Years After Extremely Preterm Birth. *JAMA Pediatr* 2021. <https://doi.org/10.1001/jamapediatrics.2021.2052>.
- Cheong JL, Spittle AJ, Burnett AC, Anderson PJ, Doyle LW. Have outcomes following extremely preterm birth improved over time? *Semin Fetal Neonatal Med* 2020;25:101114. <https://doi.org/10.1016/j.siny.2020.101114>.
- Cheung PC, Franks PA, Kramer MR, Kay CM, Drews-Botsch CD, Welsh JA, et al. Elementary school physical activity opportunities and physical fitness of students: A statewide cross-sectional study of schools. *PloS One* 2019;14:e0210444. <https://doi.org/10.1371/journal.pone.0210444>.
- Chorna O, Cioni G, Guzzetta A. Principles of early intervention. *Handb Clin Neurol* 2020;174:333–41. <https://doi.org/10.1016/B978-0-444-64148-9.00024-7>.
- Cohen J. Statistical power analysis for the behavioral sciences. vol. Second Edition. New York University: Lawrence Erlbaum Associates; 1988.
- Collins LM, Schafer JL, Kam CM. A comparison of inclusive and restrictive strategies in modern missing data procedures. *Psychol Methods* 2001;6:330–51.
- Costa DS, Miranda DM, Burnett AC, Doyle LW, Cheong JLY, Anderson PJ, et al. Executive Function and Academic Outcomes in Children Who Were Extremely Preterm. *Pediatrics* 2017;140:e20170257. <https://doi.org/10.1542/peds.2017-0257>.
- Costa R, Aubert AM, Seppänen A-V, Ådén U, Sarrechia I, Zemlin M, et al. Prediction of movement difficulties at 5 years from parent report at 2 years in children born extremely preterm. *Dev Med Child Neurol* 2023. <https://doi.org/10.1111/dmcn.15518>.
- Costa R, Aubert AM, Seppänen A-V, Ådén U, Sarrechia L, Zemlin M, et al. Motor-related health care for 5-year-old children born extremely preterm with movement impairments. *Dev Med Child Neurol* 2022. <https://doi.org/10.1111/dmcn.15202>.
- Costa R, Johnson S, Cuttini M, Pierrat V, Sarrechia I, Barros H, et al. The impact of choice of norms on classification of motor impairment for children born very preterm. *Early Hum Dev* 2020;105056. <https://doi.org/10.1016/j.earlhumdev.2020.105056>.
- Croft S, Stride C, Maughan B, Rowe R. Validity of the strengths and difficulties questionnaire in preschool-aged children. *Pediatrics* 2015;135:e1210-1219. <https://doi.org/10.1542/peds.2014-2920>.
- Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol* 2003;56:395–407. [https://doi.org/10.1016/s0895-4356\(03\)00044-1](https://doi.org/10.1016/s0895-4356(03)00044-1).
- Daugbjerg SB, Kahlmeier S, Racioppi F, Martin-Diener E, Martin B, Oja P, et al. Promotion of physical activity in the European region: content analysis of 27 national policy documents. *J Phys Act Health* 2009;6:805–17. <https://doi.org/10.1123/jpah.6.6.805>.
- Davis E, Waters E, Mackinnon A, Reddihough D, Graham HK, Mehmet-Radji O, et al. Paediatric quality of life instruments: a review of the impact of the conceptual framework on outcomes. *Dev Med Child Neurol* 2006;48:311–8. <https://doi.org/10.1017/S0012162206000673>.

- Davis NM, Ford GW, Anderson PJ, Doyle LW. Developmental coordination disorder at 8 years of age in a regional cohort of extremely-low-birthweight or very preterm infants. *Dev Med Child Neurol* 2007;49:325–30. <https://doi.org/10.1111/j.1469-8749.2007.00325.x>.
- Dellatolas G, De Agostini M, Curt F, Kremin H, Letierce A, Maccario J, et al. Manual skill, hand skill asymmetry, and cognitive performances in young children. *Laterality* 2003;8:317–38. <https://doi.org/10.1080/13576500342000121>.
- Delnord M, Zeitlin J. Epidemiology of late preterm and early term births - An international perspective. *Semin Fetal Neonatal Med* 2019;24:3–10. <https://doi.org/10.1016/j.siny.2018.09.001>.
- Demeši Drljan Č, Mikov A, Filipović K, Tomašević-Todorović S, Knežević A, Krasnik R. Cerebral palsy in preterm infants. *Vojnosanit Pregl* 2016;73:343–8. <https://doi.org/10.2298/VSP140321019D>.
- Dewar R, Love S, Johnston LM. Exercise interventions improve postural control in children with cerebral palsy: a systematic review. *Dev Med Child Neurol* 2015;57:504–20. <https://doi.org/10.1111/dmcn.12660>.
- Dewey D, Creighton DE, Heath JA, Wilson BN, Anseeuw-Deeks D, Crawford SG, et al. Assessment of Developmental Coordination Disorder in Children Born With Extremely Low Birth Weights. *Dev Neuropsychol* 2011;36:42–56. <https://doi.org/10.1080/87565641.2011.540535>.
- Dewey D, Thompson DK, Kelly CE, Spittle AJ, Cheong JLY, Doyle LW, et al. Very preterm children at risk for developmental coordination disorder have brain alterations in motor areas. *Acta Paediatr* 2019;108:1649–60. <https://doi.org/10.1111/apa.14786>.
- Diamond A. Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. *Child Dev* 2000;71:44–56. <https://doi.org/10.1111/1467-8624.00117>.
- Dickinson HO, Parkinson KN, Ravens-Sieberer U, Schirripa G, Thyen U, Arnaud C, et al. Self-reported quality of life of 8-12-year-old children with cerebral palsy: a cross-sectional European study. *Lancet Lond Engl* 2007;369:2171–8. [https://doi.org/10.1016/S0140-6736\(07\)61013-7](https://doi.org/10.1016/S0140-6736(07)61013-7).
- Doyle LW, Anderson PJ. Adult outcome of extremely preterm infants. *Pediatrics* 2010;126:342–51. <https://doi.org/10.1542/peds.2010-0710>.
- Doyle LW, Anderson PJ, Battin M, Bowen JR, Brown N, Callanan C, et al. Long term follow up of high risk children: who, why and how? *BMC Pediatr* 2014;14:279. <https://doi.org/10.1186/1471-2431-14-279>.
- Doyle LW, Spittle A, Anderson PJ, Cheong JL. School-aged neurodevelopmental outcomes for children born extremely preterm. *Arch Dis Child* 2021;106:834–8. <https://doi.org/10.1136/archdischild-2021-321668>.
- Draper ES, Manktelow BN, Cuttini M, Maier RF, Fenton AC, Van Reempts P, et al. Variability in Very Preterm Stillbirth and In-Hospital Mortality Across Europe. *Pediatrics* 2017;139. <https://doi.org/10.1542/peds.2016-1990>.
- Drotar D. Validating measures of pediatric health status, functional status, and health-related quality of life: key methodological challenges and strategies. *Ambul Pediatr Off J Ambul Pediatr Assoc* 2004;4:358–64. <https://doi.org/10.1367/A03-101R.1>.

- Dyett LE, Kennea N, Counsell SJ, Maalouf EF, Ajayi-Obe M, Duggan PJ, et al. Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment. *Pediatrics* 2006;118:536–48. <https://doi.org/10.1542/peds.2005-1866>.
- Edstedt Bonamy AK, Zeitlin J, Piedvache A, Maier RF, van Heijst A, Varendi H, et al. Wide variation in severe neonatal morbidity among very preterm infants in European regions. *Arch Dis Child Fetal Neonatal Ed* 2019;104:F36–45. <https://doi.org/10.1136/archdischild-2017-313697>.
- Edwards J, Berube M, Erlandson K, Haug S, Johnstone H, Meagher M, et al. Developmental coordination disorder in school-aged children born very preterm and/or at very low birth weight: a systematic review. *J Dev Behav Pediatr JDBP* 2011;32:678–87. <https://doi.org/10.1097/DBP.0b013e31822a396a>.
- Eiser C. Use of quality of life measures in clinical trials. *Ambul Pediatr Off J Ambul Pediatr Assoc* 2004;4:395–9. <https://doi.org/10.1367/A03-112R.1>.
- Eiser C, Morse R. The measurement of quality of life in children: past and future perspectives. *J Dev Behav Pediatr JDBP* 2001a;22:248–56. <https://doi.org/10.1097/00004703-200108000-00007>.
- Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil* 2001b;10:347–57. <https://doi.org/10.1023/a:1012253723272>.
- European Foundation for the Care of Newborn Infants. Retinopathy of Prematurity (ROP). EFCNI 2020. <https://www.efcni.org/activities/efcni-academy/retinopathy-of-prematurity-rop/> (accessed February 24, 2023).
- European Foundation for the Care of Newborn Infants. European Standards of Care for Newborn Health. 2018.
- European Union. EU Physical Activity Guidelines: Recommended Policy Actions in Support of Health-Enhancing Physical Activity. 2008.
- Euro-Peristat. European Perinatal Health Report. Core indicators of the health and care of pregnant women and babies in Europe from 2015 to 2019. <https://www.europeristat.com/>: 2022.
- Evensen KAI, Ustad T, Tikanmäki M, Haaramo P, Kajantie E. Long-term motor outcomes of very preterm and/or very low birth weight individuals without cerebral palsy: A review of the current evidence. *Semin Fetal Neonatal Med* 2020;25:101116. <https://doi.org/10.1016/j.siny.2020.101116>.
- Faught BE, Hay JA, Cairney J, Flouris A. Increased risk for coronary vascular disease in children with developmental coordination disorder. *J Adolesc Health Off Publ Soc Adolesc Med* 2005;37:376–80. <https://doi.org/10.1016/j.jadohealth.2004.09.021>.
- Fayers P, Machin D. Quality of Life: The assessment, analysis and interpretation of patient-reported outcomes. John Wiley & Sons; 2007.
- Ferrari F, Gallo C, Pugliese M, Guidotti I, Gavioli S, Coccolini E, et al. Preterm birth and developmental problems in the preschool age. Part I: minor motor problems. *J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet* 2012;25:2154–9. <https://doi.org/10.3109/14767058.2012.696164>.

- Ferreira L, Godinez I, Gabbard C, Vieira JLL, Caçola P. Motor development in school-age children is associated with the home environment including socioeconomic status. *Child Care Health Dev* 2018;44:801–6. <https://doi.org/10.1111/cch.12606>.
- Ferreira PL, Ferreira LN, Pereira LN. How consistent are health utility values? *Qual Life Res Int J Qual Life Asp Treat Care Rehabil* 2008;17:1031–42. <https://doi.org/10.1007/s11136-008-9368-8>.
- Flapper BCT, Schoemaker MM. Effects of methylphenidate on quality of life in children with both developmental coordination disorder and ADHD. *Dev Med Child Neurol* 2008;50:294–9. <https://doi.org/10.1111/j.1469-8749.2008.02039.x>.
- Galea C, McIntyre S, Smithers-Sheedy H, Reid SM, Gibson C, Delacy M, et al. Cerebral palsy trends in Australia (1995-2009): a population-based observational study. *Dev Med Child Neurol* 2019;61:186–93. <https://doi.org/10.1111/dmcn.14011>.
- Ghassabian A, Sundaram R, Bell E, Bello SC, Kus C, Yeung E. Gross Motor Milestones and Subsequent Development. *Pediatrics* 2016;138:e20154372. <https://doi.org/10.1542/peds.2015-4372>.
- Gibson A-M, Doyle LW. Respiratory outcomes for the tiniest or most immature infants. *Semin Fetal Neonatal Med* 2014;19:105–11. <https://doi.org/10.1016/j.siny.2013.10.006>.
- Gibson JJ. *The Ecological Approach to Visual Perception*. New York: Psychology Press; 2014. <https://doi.org/10.4324/9781315740218>.
- Gilard V, Tebani A, Bekri S, Marret S. Intraventricular Hemorrhage in Very Preterm Infants: A Comprehensive Review. *J Clin Med* 2020;9:2447. <https://doi.org/10.3390/jcm9082447>.
- Gire C, Resseguier N, Brévaut-Malaty V, Marret S, Cambonie G, Souksi-Medioni I, et al. Quality of life of extremely preterm school-age children without major handicap: a cross-sectional observational study. *Arch Dis Child* 2019;104:333–9. <https://doi.org/10.1136/archdischild-2018-315046>.
- Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet Lond Engl* 2008;371:75–84. [https://doi.org/10.1016/S0140-6736\(08\)60074-4](https://doi.org/10.1016/S0140-6736(08)60074-4).
- Goodman R. Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry* 2001;40:1337–45. <https://doi.org/10.1097/00004583-200111000-00015>.
- Goodman R. The Strengths and Difficulties Questionnaire: a research note. *J Child Psychol Psychiatry* 1997;38:581–6. <https://doi.org/10.1111/j.1469-7610.1997.tb01545.x>.
- Gorter JW, Ketelaar M, Rosenbaum P, Hadders PJM, Palisano R. Use of the GMFCS in infants with CP: the need for reclassification at age 2 years or older. *Dev Med Child Neurol* 2009;51:46–52. <https://doi.org/10.1111/j.1469-8749.2008.03117.x>.
- Goyen T-A, Lui K. Developmental coordination disorder in “apparently normal” schoolchildren born extremely preterm. *Arch Dis Child* 2009;94:298–302. <https://doi.org/10.1136/adc.2007.134692>.
- Greene WH. *Econometric analysis*. vol. Seventh Edition. Pearson. New York University: 2012.
- Gueze RH, Jongmans MJ, Schoemaker MM, Smits-Engelsman B. Clinical and research diagnostic criteria for developmental coordination disorder: a review and discussion. *Hum Mov Sci* 2001;20:7–47. [https://doi.org/10.1016/s0167-9457\(01\)00027-6](https://doi.org/10.1016/s0167-9457(01)00027-6).

- Hack M, Forrest CB, Schluchter M, Taylor HG, Drotar D, Holmbeck G, et al. Health status of extremely low-birth-weight children at 8 years of age: child and parent perspective. *Arch Pediatr Adolesc Med* 2011;165:922–7. <https://doi.org/10.1001/archpediatrics.2011.149>.
- Hadchouel A, Rousseau J, Rozé J-C, Arnaud C, Bellino A, Couderc L, et al. Association between asthma and lung function in adolescents born very preterm: results of the EPIPAGE cohort study. *Thorax* 2018;73:1174–6. <https://doi.org/10.1136/thoraxjnl-2017-211115>.
- Hadders-Algra M, Boxum AG, Hielkema T, Hamer EG. Effect of early intervention in infants at very high risk of cerebral palsy: a systematic review. *Dev Med Child Neurol* 2017;59:246–58. <https://doi.org/10.1111/dmcn.13331>.
- Hafström M, Källén K, Serenius F, Maršál K, Rehn E, Drake H, et al. Cerebral Palsy in Extremely Preterm Infants. *Pediatrics* 2018;141:e20171433. <https://doi.org/10.1542/peds.2017-1433>.
- Harris SR, Mickelson ECR, Zwicker JG. Diagnosis and management of developmental coordination disorder. *CMAJ Can Med Assoc J J Assoc Medicale Can* 2015;187:659–65. <https://doi.org/10.1503/cmaj.140994>.
- Haute Autorité de Santé. Recommandation de bonne pratique, troubles du neurodéveloppement: Repérage et orientation des enfants à risque. Paris: 2020.
- Henderson SE, Sugden DA. Movement Assessment Battery for Children. Psychological corporation. London, United Kingdom: 1992.
- Henderson SE, Sugden DA, Barnett AL. Movement Assessment Battery for Children-2 (2nd ed.). Psychological corporation. London, United Kingdom: 2007.
- Hennessy EM, Bracewell MA, Wood N, Wolke D, Costeloe K, Gibson A, et al. Respiratory health in pre-school and school age children following extremely preterm birth. *Arch Dis Child* 2008;93:1037–43. <https://doi.org/10.1136/adc.2008.140830>.
- Hilliard ME, Lawrence JM, Modi AC, Anderson A, Crume T, Dolan LM, et al. Identification of minimal clinically important difference scores of the PedsQL in children, adolescents, and young adults with type 1 and type 2 diabetes. *Diabetes Care* 2013a;36:1891–7. <https://doi.org/10.2337/dc12-1708>.
- Hilliard ME, Lawrence JM, Modi AC, Anderson A, Crume T, Dolan LM, et al. Identification of minimal clinically important difference scores of the PedsQL in children, adolescents, and young adults with type 1 and type 2 diabetes. *Diabetes Care* 2013b;36:1891–7. <https://doi.org/10.2337/dc12-1708>.
- Hills AP, Dengel DR, Lubans DR. Supporting public health priorities: recommendations for physical education and physical activity promotion in schools. *Prog Cardiovasc Dis* 2015;57:368–74. <https://doi.org/10.1016/j.pcad.2014.09.010>.
- Himmelman K, Beckung E, Hagberg G, Uvebrant P. Gross and fine motor function and accompanying impairments in cerebral palsy. *Dev Med Child Neurol* 2006;48:417–23. <https://doi.org/10.1017/S0012162206000922>.
- Himpens E, Oostra A, Franki I, Van Maele G, Vanhaesebrouck P, Van den Broeck C. Predictability of cerebral palsy and its characteristics through neonatal cranial ultrasound in a high-risk NICU population. *Eur J Pediatr* 2010;169:1213–9. <https://doi.org/10.1007/s00431-010-1207-6>.

- Himpens E, Van den Broeck C, Oostra A, Calders P, Vanhaesebrouck P. Prevalence, type, distribution, and severity of cerebral palsy in relation to gestational age: a meta-analytic review. *Dev Med Child Neurol* 2008;50:334–40. <https://doi.org/10.1111/j.1469-8749.2008.02047.x>.
- Hintz SR, Barnes PD, Bulas D, Slovis TL, Finer NN, Wrage LA, et al. Neuroimaging and neurodevelopmental outcome in extremely preterm infants. *Pediatrics* 2015;135:e32–42. <https://doi.org/10.1542/peds.2014-0898>.
- Hirvonen M, Ojala R, Korhonen P, Haataja P, Eriksson K, Gissler M, et al. Visual and Hearing Impairments After Preterm Birth. *Pediatrics* 2018;142:e20173888. <https://doi.org/10.1542/peds.2017-3888>.
- Hollebrandse NL, Spittle AJ, Burnett AC, Anderson PJ, Roberts G, Doyle LW, et al. School-age outcomes following intraventricular haemorrhage in infants born extremely preterm. *Arch Dis Child Fetal Neonatal Ed* 2021;106:4–8. <https://doi.org/10.1136/archdischild-2020-318989>.
- Holsti L, Grunau RVE, Whitfield MF. Developmental coordination disorder in extremely low birth weight children at nine years. *J Dev Behav Pediatr JDBP* 2002;23:9–15. <https://doi.org/10.1097/00004703-200202000-00002>.
- van Hoorn JF, Schoemaker MM, Stuive I, Dijkstra PU, Rodrigues Trigo Pereira F, van der Sluis CK, et al. Risk factors in early life for developmental coordination disorder: a scoping review. *Dev Med Child Neurol* 2021;63:511–9. <https://doi.org/10.1111/dmcn.14781>.
- de Hóra N, Larkin L, Connell A. Is Group-Based or Individual-Based Intervention more Effective for Quality of Life Outcomes in Children with Developmental Coordination Disorder? A Systematic Review. *Phys Occup Ther Pediatr* 2019;39:353–72. <https://doi.org/10.1080/01942638.2018.1490847>.
- Huber PJ. The behavior of maximum likelihood estimates under nonstandard conditions. *Proc Fifth Berkeley Symp Math Stat Probab Vol 1 Stat* 1967;5.1:221–34.
- Huhtala M, Korja R, Rautava L, Lehtonen L, Haataja L, Lapinleimu H, et al. Health-related quality of life in very low birth weight children at nearly eight years of age. *Acta Paediatr Oslo Nor* 1992 2016;105:53–9. <https://doi.org/10.1111/apa.13241>.
- Husby IM, Stray KM-T, Olsen A, Lydersen S, Indredavik MS, Brubakk A-M, et al. Long-term follow-up of mental health, health-related quality of life and associations with motor skills in young adults born preterm with very low birth weight. *Health Qual Life Outcomes* 2016;14:56. <https://doi.org/10.1186/s12955-016-0458-y>.
- Hutchinson EA, Luca CRD, Doyle LW, Roberts G, Anderson PJ, Group for the VICS. School-age Outcomes of Extremely Preterm or Extremely Low Birth Weight Children. *Pediatrics* 2013;131:e1053–61. <https://doi.org/10.1542/peds.2012-2311>.
- Iams JD, Romero R, Culhane JF, Goldenberg RL. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. *Lancet Lond Engl* 2008;371:164–75. [https://doi.org/10.1016/S0140-6736\(08\)60108-7](https://doi.org/10.1016/S0140-6736(08)60108-7).
- Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study. *J Pediatr* 2003;143:171–9. [https://doi.org/10.1067/S0022-3476\(03\)00357-3](https://doi.org/10.1067/S0022-3476(03)00357-3).

- Jansen L, van Steenis A, van den Berg-Huysmans AA, Wiggers-de Bruine ST, Rijken M, de Vries LS, et al. Associations between Neonatal Magnetic Resonance Imaging and Short- and Long-Term Neurodevelopmental Outcomes in a Longitudinal Cohort of Very Preterm Children. *J Pediatr* 2021;234:46-53.e2. <https://doi.org/10.1016/j.jpeds.2021.02.005>.
- Jardine J, Glinianaia SV, McConachie H, Embleton ND, Rankin J. Self-reported quality of life of young children with conditions from early infancy: a systematic review. *Pediatrics* 2014;134:e1129-1148. <https://doi.org/10.1542/peds.2014-0352>.
- Jarjour IT. Neurodevelopmental outcome after extreme prematurity: a review of the literature. *Pediatr Neurol* 2015;52:143-52. <https://doi.org/10.1016/j.pediatrneurol.2014.10.027>.
- Jeukens-Visser M, Koldewijn K, van Wassenaer-Leemhuis AG, Flierman M, Nollet F, Wolf M-J. Development and nationwide implementation of a postdischarge responsive parenting intervention program for very preterm born children: The TOP program. *Infant Ment Health J* 2021;42:423-37. <https://doi.org/10.1002/imhj.21902>.
- Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723-9. <https://doi.org/10.1164/ajrccm.163.7.2011060>.
- Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in the EPICure study. *J Am Acad Child Adolesc Psychiatry* 2010;49:453-463.e1.
- Johnson S, Marlow N. Preterm birth and childhood psychiatric disorders. *Pediatr Res* 2011;69:11R-8R. <https://doi.org/10.1203/PDR.0b013e318212faa0>.
- 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* 2019;84:85-95. <https://doi.org/10.1016/j.ridd.2018.05.012>.
- Kelly CE, Chan L, Burnett AC, Lee KJ, Connelly A, Anderson PJ, et al. Brain structural and microstructural alterations associated with cerebral palsy and motor impairments in adolescents born extremely preterm and/or extremely low birthweight. *Dev Med Child Neurol* 2015;57:1168-75. <https://doi.org/10.1111/dmcn.12854>.
- van Kessel-Feddema B, Sondaar M, de Kleine M, Verhaak C, van Baar A. Concordance between school outcomes and developmental follow-up results of very preterm and/or low birth weight children at the age of 5 years. *Eur J Pediatr* 2007;166:693-9. <https://doi.org/10.1007/s00431-006-0309-7>.
- Ketharanathan N, Lee W, de Mol AC. Health-related quality of life, emotional and behavioral problems in mild to moderate prematures at (pre-)school age. *Early Hum Dev* 2011;87:705-9. <https://doi.org/10.1016/j.earlhumdev.2011.05.011>.
- Keunen K, Išgum I, van Kooij BJM, Anbeek P, van Haastert IC, Koopman-Esseboom C, et al. Brain Volumes at Term-Equivalent Age in Preterm Infants: Imaging Biomarkers for Neurodevelopmental Outcome through Early School Age. *J Pediatr* 2016;172:88-95. <https://doi.org/10.1016/j.jpeds.2015.12.023>.
- de Kieviet JF, Piek JP, Aarnoudse-Moens CS, Oosterlaan J. Motor development in very preterm and very low-birth-weight children from birth to adolescence: a meta-analysis. *JAMA* 2009;302:2235-42. <https://doi.org/10.1001/jama.2009.1708>.

- Kirby RS, Wingate MS, Van Naarden Braun K, Doernberg NS, Arneson CL, Benedict RE, et al. Prevalence and functioning of children with cerebral palsy in four areas of the United States in 2006: a report from the Autism and Developmental Disabilities Monitoring Network. *Res Dev Disabil* 2011;32:462–9. <https://doi.org/10.1016/j.ridd.2010.12.042>.
- Koenker R. *Quantile regression*. Cambridge University Press; 2005.
- Koldewijn K, Wolf M-J, van Wassenaer A, Beelen A, de Groot IJM, Hedlund R. The Infant Behavioral Assessment and Intervention Program to support preterm infants after hospital discharge: a pilot study. *Dev Med Child Neurol* 2005;47:105–12. <https://doi.org/10.1017/s0012162205000198>.
- Korzeniewski SJ, Slaughter J, Lenski M, Haak P, Paneth N. The complex aetiology of cerebral palsy. *Nat Rev Neurol* 2018;14:528–43. <https://doi.org/10.1038/s41582-018-0043-6>.
- Laucht M, Esser G, Schmidt MH. Developmental outcome of infants born with biological and psychosocial risks. *J Child Psychol Psychiatry* 1997;38:843–53. <https://doi.org/10.1111/j.1469-7610.1997.tb01602.x>.
- Lean RE, Paul RA, Smyser TA, Smyser CD, Rogers CE. Social Adversity and Cognitive, Language and Motor Development of Very Preterm Children from 2 to 5 Years of Age. *J Pediatr* 2018;203:177–184.e1. <https://doi.org/10.1016/j.jpeds.2018.07.110>.
- Leggett LE, Khadaroo RG, Holroyd-Leduc J, Lorenzetti DL, Hanson H, Wagg A, et al. Measuring Resource Utilization: A Systematic Review of Validated Self-Reported Questionnaires. *Medicine (Baltimore)* 2016;95:e2759. <https://doi.org/10.1097/MD.0000000000002759>.
- Li Q, Kinsman SL, Jenkins DD, Hovell MF, Ryan RM. Decreasing prevalence of cerebral palsy in birth cohorts in South Carolina using Medicaid, disability service, and hospital discharge data, 1996 to 2009. *Dev Med Child Neurol* 2019;61:593–600. <https://doi.org/10.1111/dmcn.14085>.
- Li Y-C, Graham JD, Cairney J. Moderating Effects of Physical Activity and Global Self-Worth on Internalizing Problems in School-Aged Children With Developmental Coordination Disorder. *Front Psychol* 2018;9. <https://doi.org/10.3389/fpsyg.2018.01740>.
- van Lieshout P, Candundo H, Martino R, Shin S, Barakat-Haddad C. Onset factors in cerebral palsy: A systematic review. *Neurotoxicology* 2017;61:47–53. <https://doi.org/10.1016/j.neuro.2016.03.021>.
- Linsell L, Malouf R, Morris J, Kurinczuk JJ, Marlow N. Prognostic factors for cerebral palsy and motor impairment in children born very preterm or very low birthweight: a systematic review. *Dev Med Child Neurol* 2016;58:554–69. <https://doi.org/10.1111/dmcn.12972>.
- Luu TM, Vohr BR, Allan W, Schneider KC, Ment LR. Evidence for catch-up in cognition and receptive vocabulary among adolescents born very preterm. *Pediatrics* 2011;128:313–22. <https://doi.org/10.1542/peds.2010-2655>.
- Maas CJM, Hox JJ. Robustness issues in multilevel regression analysis. *Stat Neerlandica* 2004;58:127–37. <https://doi.org/10.1046/j.0039-0402.2003.00252.x>.
- Majnemer A. Motor incoordination in children born preterm: coordinated efforts needed. *Dev Med Child Neurol* 2007;49:324. <https://doi.org/10.1111/j.1469-8749.2007.00324.x>.
- Makris T, Dorstyn D, Crettenden A. Quality of life in children and adolescents with cerebral palsy: a systematic review with meta-analysis. *Disabil Rehabil* 2021;43:299–308. <https://doi.org/10.1080/09638288.2019.1623852>.

- Mangin KS, Horwood LJ, Woodward LJ. Cognitive Development Trajectories of Very Preterm and Typically Developing Children. *Child Dev* 2017;88:282–98. <https://doi.org/10.1111/cdev.12585>.
- 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;352:9–19. <https://doi.org/10.1056/NEJMoa041367>.
- Marquet-Doléac J, Soppelsa R, Albaret J-M. Movement Assessment Battery for Children-2, French Adaptation, 2nd ed. Pearson France-ECPA. France: 2016.
- Masten AS, Lucke CM, Nelson KM, Stallworthy IC. Resilience in Development and Psychopathology: Multisystem Perspectives. *Annu Rev Clin Psychol* 2021;17:521–49. <https://doi.org/10.1146/annurev-clinpsy-081219-120307>.
- Matthews TJ, MacDorman MF, Thoma ME. Infant Mortality Statistics From the 2013 Period Linked Birth/Infant Death Data Set. *Natl Vital Stat Rep Cent Dis Control Prev Natl Cent Health Stat Natl Vital Stat Syst* 2015;64:1–30.
- McIntyre S, Morgan C, Walker K, Novak I. Cerebral palsy--don't delay. *Dev Disabil Res Rev* 2011;17:114–29. <https://doi.org/10.1002/ddrr.1106>.
- Micceri T. The unicorn, the normal curve, and other improbable creatures. *Psychol Bull* 1989;105:156–66. <https://doi.org/10.1037/0033-2909.105.1.156>.
- Miller SP, Ferriero DM, Leonard C, Piecuch R, Glidden DV, Partridge JC, et al. Early brain injury in premature newborns detected with magnetic resonance imaging is associated with adverse early neurodevelopmental outcome. *J Pediatr* 2005;147:609–16. <https://doi.org/10.1016/j.jpeds.2005.06.033>.
- Missiuna C, Moll S, Law M, King S, King G. Mysteries and mazes: parents' experiences of children with developmental coordination disorder. *Can J Occup Ther Rev Can Ergother* 2006;73:7–17. <https://doi.org/10.2182/cjot.05.0010>.
- Miyahara M, Hillier SL, Pridham L, Nakagawa S. Task-oriented interventions for children with developmental co-ordination disorder. *Cochrane Database Syst Rev* 2017;7:CD010914. <https://doi.org/10.1002/14651858.CD010914.pub2>.
- Molloy CS, Wilson-Ching M, Anderson VA, Roberts G, Anderson PJ, Doyle LW, et al. Visual processing in adolescents born extremely low birth weight and/or extremely preterm. *Pediatrics* 2013;132:e704-712. <https://doi.org/10.1542/peds.2013-0040>.
- Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, Costeloe KL, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. *BMJ* 2012;345:e7961. <https://doi.org/10.1136/bmj.e7961>.
- Moreira RS, Magalhães LC, Alves CRL. Effect of preterm birth on motor development, behavior, and school performance of school-age children: a systematic review. *J Pediatr (Rio J)* 2014;90:119–34. <https://doi.org/10.1016/j.jpeds.2013.05.010>.
- Morgan AS, Zeitlin J, Källén K, Draper ES, Maršál K, Norman M, et al. Birth outcomes between 22 and 26 weeks' gestation in national population-based cohorts from Sweden, England and France. *Acta Paediatr Oslo Nor* 1992 2022;111:59–75. <https://doi.org/10.1111/apa.16084>.
- Morgan C, Fetters L, Adde L, Badawi N, Bancale A, Boyd RN, et al. Early Intervention for Children Aged 0 to 2 Years With or at High Risk of Cerebral Palsy: International Clinical

- Practice Guideline Based on Systematic Reviews. *JAMA Pediatr* 2021;175:846–58. <https://doi.org/10.1001/jamapediatrics.2021.0878>.
- Mottram R, Holt J. “Is gestational age a factor in determining the health-related quality of life of children and young people born preterm?” A critical review of the literature. *J Neonatal Nurs* 2010;16:80–90. <https://doi.org/10.1016/j.jnn.2009.10.004>.
- Murthy P, Zein H, Thomas S, Scott JN, Abou Mehrem A, Esser MJ, et al. Neuroprotection Care Bundle Implementation to Decrease Acute Brain Injury in Preterm Infants. *Pediatr Neurol* 2020;110:42–8. <https://doi.org/10.1016/j.pediatrneurol.2020.04.016>.
- 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. <https://doi.org/10.1016/j.earlhumdev.2016.11.002>.
- National Institute for Health and Care Excellence. Developmental follow-up of children and young people born preterm. 2017a.
- National Institute for Health and Care Excellence. Cerebral palsy in under 25s: assessment and management. NICE; 2017b.
- Novak I, Hines M, Goldsmith S, Barclay R. Clinical prognostic messages from a systematic review on cerebral palsy. *Pediatrics* 2012;130:e1285-1312. <https://doi.org/10.1542/peds.2012-0924>.
- Novak I, Honan I. Effectiveness of paediatric occupational therapy for children with disabilities: A systematic review. *Aust Occup Ther J* 2019;66:258–73. <https://doi.org/10.1111/1440-1630.12573>.
- Novak I, McIntyre S, Morgan C, Campbell L, Dark L, Morton N, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. *Dev Med Child Neurol* 2013;55:885–910. <https://doi.org/10.1111/dmcn.12246>.
- Nuytten A, Behal H, Duhamel A, Jarreau P-H, Mazela J, Milligan D, et al. Evidence-Based Neonatal Unit Practices and Determinants of Postnatal Corticosteroid-Use in Preterm Births below 30 Weeks GA in Europe. A Population-Based Cohort Study. *PloS One* 2017;12:e0170234. <https://doi.org/10.1371/journal.pone.0170234>.
- O’Reilly H, Johnson S, Ni Y, Wolke D, Marlow N. Neuropsychological Outcomes at 19 Years of Age Following Extremely Preterm Birth. *Pediatrics* 2020;145. <https://doi.org/10.1542/peds.2019-2087>.
- Orton JL, Olsen JE, Ong K, Lester R, Spittle AJ. NICU Graduates: The Role of the Allied Health Team in Follow-Up. *Pediatr Ann* 2018;47:e165–71. <https://doi.org/10.3928/19382359-20180325-02>.
- O’Shea TM. Diagnosis, treatment, and prevention of cerebral palsy. *Clin Obstet Gynecol* 2008;51:816–28. <https://doi.org/10.1097/GRF.0b013e3181870ba7>.
- Oskoui M, Coutinho F, Dykeman J, Jetté N, Pringsheim T. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. *Dev Med Child Neurol* 2013;55:509–19. <https://doi.org/10.1111/dmcn.12080>.
- Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol Off J Am Soc Clin Oncol* 1998;16:139–44. <https://doi.org/10.1200/JCO.1998.16.1.139>.

- Oudgenoeg-Paz O, Mulder H, Jongmans MJ, van der Ham IJM, Van der Stigchel S. The link between motor and cognitive development in children born preterm and/or with low birth weight: A review of current evidence. *Neurosci Biobehav Rev* 2017;80:382–93. <https://doi.org/10.1016/j.neubiorev.2017.06.009>.
- Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214–23. <https://doi.org/10.1111/j.1469-8749.1997.tb07414.x>.
- Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978;92:529–34. [https://doi.org/10.1016/s0022-3476\(78\)80282-0](https://doi.org/10.1016/s0022-3476(78)80282-0).
- 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;60:342–55. <https://doi.org/10.1111/dmcn.13675>.
- Patel RM. Short- and Long-Term Outcomes for Extremely Preterm Infants. *Am J Perinatol* 2016;33:318–28. <https://doi.org/10.1055/s-0035-1571202>.
- Pearsall-Jones JG, Piek JP, Levy F. Developmental Coordination Disorder and cerebral palsy: Categories or a continuum? *Hum Mov Sci* 2010;29:787–98. <https://doi.org/10.1016/j.humov.2010.04.006>.
- Pearl S, Cheong JLY, Roberts G, Davis N, Anderson PJ, Doyle LW, et al. Changes over time in quality of life of school-aged children born extremely preterm: 1991–2005. *Arch Dis Child Fetal Neonatal Ed* 2021;106:425–9. <https://doi.org/10.1136/archdischild-2020-320582>.
- Pereira S, Bastos F, Santos C, Maia J, Tani G, Robinson LE, et al. Variation and Predictors of Gross Motor Coordination Development in Azorean Children: A Quantile Regression Approach. *Int J Environ Res Public Health* 2022;19:5417. <https://doi.org/10.3390/ijerph19095417>.
- Petscher Y, Logan JAR. Quantile regression in the study of developmental sciences. *Child Dev* 2014;85:861–81. <https://doi.org/10.1111/cdev.12190>.
- Pierrat V, Marchand-Martin L, Arnaud C, Kaminski M, Resche-Rigon M, Lebeaux C, et al. Neurodevelopmental outcome at 2 years for preterm children born at 22 to 34 weeks' gestation in France in 2011: EPIPAGE-2 cohort study. *BMJ* 2017;358:j3448. <https://doi.org/10.1136/bmj.j3448>.
- Pierrat V, Marchand-Martin L, Marret S, Arnaud C, Benhammou V, Cambonie G, et al. Neurodevelopmental outcomes at age 5 among children born preterm: EPIPAGE-2 cohort study. *BMJ* 2021;373:n741. <https://doi.org/10.1136/bmj.n741>.
- Pieters S, De Block K, Scheiris J, Eysen M, Desoete A, Deboutte D, et al. How common are motor problems in children with a developmental disorder: rule or exception? *Child Care Health Dev* 2012;38:139–45. <https://doi.org/10.1111/j.1365-2214.2011.01225.x>.
- Platt MJ, Cans C, Johnson A, Surman G, Topp M, Torrioli MG, 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 Lond Engl* 2007;369:43–50. [https://doi.org/10.1016/S0140-6736\(07\)60030-0](https://doi.org/10.1016/S0140-6736(07)60030-0).

- Potharst ES, Wassenaar AG van, Houtzager BA, Hus JWP van, Last BF, Kok JH. High Incidence of Multi-Domain Disabilities in Very Preterm Children at Five Years of Age. *J Pediatr* 2011;159:79–85. <https://doi.org/10.1016/j.jpeds.2010.12.055>.
- Powell JL. Least absolute deviations estimation for the censored regression model. *J Econom* 1984;25:303–25. [https://doi.org/10.1016/0304-4076\(84\)90004-6](https://doi.org/10.1016/0304-4076(84)90004-6).
- Qasemi Z, Yaseri M, Hosseini M. Selection of Appropriate Model for Quality of Life Data of Strabismus Patients Despite Censorship. *J Biostat Epidemiol* 2020;6:221–33. <https://doi.org/10.18502/jbe.v6i3.5108>.
- Ravens-Sieberer U, Erhart M, Wille N, Wetzel R, Nickel J, Bullinger M. Generic health-related quality-of-life assessment in children and adolescents: methodological considerations. *PharmacoEconomics* 2006;24:1199–220. <https://doi.org/10.2165/00019053-200624120-00005>.
- Ream MA, Lehwald L. Neurologic Consequences of Preterm Birth. *Curr Neurol Neurosci Rep* 2018;18:48. <https://doi.org/10.1007/s11910-018-0862-2>.
- Rees S, Inder T. Fetal and neonatal origins of altered brain development. *Early Hum Dev* 2005;81:753–61. <https://doi.org/10.1016/j.earlhumdev.2005.07.004>.
- Reid SM, Meehan E, McIntyre S, Goldsmith S, Badawi N, Reddiough DS, et al. Temporal trends in cerebral palsy by impairment severity and birth gestation. *Dev Med Child Neurol* 2016;58 Suppl 2:25–35. <https://doi.org/10.1111/dmcn.13001>.
- Rizzolo A, Shah PS, Boucorian I, Lemyre B, Bertelle V, Pelausa E, et al. Cumulative effect of evidence-based practices on outcomes of preterm infants born at <29 weeks' gestational age. *Am J Obstet Gynecol* 2020;222:181.e1-181.e10. <https://doi.org/10.1016/j.ajog.2019.08.058>.
- Roberts G. Quality of life after extremely preterm birth. *Arch Dis Child* 2019;104:311–2. <https://doi.org/10.1136/archdischild-2018-315708>.
- Rogers EE, Hintz SR. Early neurodevelopmental outcomes of extremely preterm infants. *Semin Perinatol* 2016;40:497–509. <https://doi.org/10.1053/j.semperi.2016.09.002>.
- Rogers W. Regression standard errors in clustered samples. *Stata Tech Bull* 1994;3.
- Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007;109:8–14.
- Rosenbaum PL, Walter SD, Hanna SE, Palisano RJ, Russell DJ, Raina P, et al. Prognosis for gross motor function in cerebral palsy: creation of motor development curves. *JAMA* 2002;288:1357–63. <https://doi.org/10.1001/jama.288.11.1357>.
- Rowen D, Brazier J, Roberts J. Mapping SF-36 onto the EQ-5D index: how reliable is the relationship? *Health Qual Life Outcomes* 2009;7:27. <https://doi.org/10.1186/1477-7525-7-27>.
- Royston P, White IR. Multiple Imputation by Chained Equations (MICE): Implementation in Stata. *J Stat Softw* 2011;45:1–20. <https://doi.org/10.18637/jss.v045.i04>.
- Saigal S. Quality of life of former premature infants during adolescence and beyond. *Early Hum Dev* 2013;89:209–13. <https://doi.org/10.1016/j.earlhumdev.2013.01.012>.

- Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet Lond Engl* 2008;371:261–9. [https://doi.org/10.1016/S0140-6736\(08\)60136-1](https://doi.org/10.1016/S0140-6736(08)60136-1).
- Saigal S, Ferro MA, Van Lieshout RJ, Schmidt LA, Morrison KM, Boyle MH. Health-Related Quality of Life Trajectories of Extremely Low Birth Weight Survivors into Adulthood. *J Pediatr* 2016;179:68-73.e1. <https://doi.org/10.1016/j.jpeds.2016.08.018>.
- Saigal S, Stoskopf BL, Feeny D, Furlong W, Burrows E, Rosenbaum PL, et al. Differences in preferences for neonatal outcomes among health care professionals, parents, and adolescents. *JAMA* 1999;281:1991–7. <https://doi.org/10.1001/jama.281.21.1991>.
- Saigal S, Tyson J. Measurement of quality of life of survivors of neonatal intensive care: critique and implications. *Semin Perinatol* 2008;32:59–66. <https://doi.org/10.1053/j.semperi.2007.12.007>.
- Schimmel MS, Bromiker R, Hammerman C, Chertman L, Ioscovich A, Granovsky-Grisaru S, et al. The effects of maternal age and parity on maternal and neonatal outcome. *Arch Gynecol Obstet* 2015;291:793–8. <https://doi.org/10.1007/s00404-014-3469-0>.
- Schmidt B, Roberts RS, Davis PG, Doyle LW, Asztalos EV, Opie G, et al. Prediction of Late Death or Disability at Age 5 Years Using a Count of 3 Neonatal Morbidities in Very Low Birth Weight Infants. *J Pediatr* 2015;167:982-986.e2. <https://doi.org/10.1016/j.jpeds.2015.07.067>.
- Scott MN, Taylor HG, Fristad MA, Klein N, Espy KA, Minich N, et al. Behavior disorders in extremely preterm/extremely low birth weight children in kindergarten. *J Dev Behav Pediatr* 2012;33:202–13. <https://doi.org/10.1097/DBP.0b013e3182475287>.
- Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res* 2013;22:278–95. <https://doi.org/10.1177/0962280210395740>.
- Seaman SR, White IR, Copas AJ, Li L. Combining Multiple Imputation and Inverse-Probability Weighting. *Biometrics* 2012;68:129–37. <https://doi.org/10.1111/j.1541-0420.2011.01666.x>.
- Seid M, Varni JW, Cummings L, Schonlau M. The impact of realized access to care on health-related quality of life: a two-year prospective cohort study of children in the California State Children’s Health Insurance Program. *J Pediatr* 2006;149:354–61. <https://doi.org/10.1016/j.jpeds.2006.04.024>.
- Sentenac M, Chaimani A, Twilhaar S, Benhammou V, Johnson S, Morgan A, et al. The challenges of heterogeneity in gestational age and birthweight inclusion criteria for research synthesis on very preterm birth and childhood cognition: An umbrella review and meta-regression analysis. *Paediatr Perinat Epidemiol* 2022;36:717–25. <https://doi.org/10.1111/ppe.12846>.
- Seppänen A-V. Impact of socioeconomic factors on follow-up and health service use up to 5 years of age in a European cohort of children born very preterm : Impact des facteurs socio-économiques sur le suivi et l’utilisation des services de santé jusqu’à l’âge de 5 ans dans une cohorte européenne d’enfants nés très prématurément. Sorbonne université, 2020.
- Seppänen A-V, Bodeau-Livinec F, Boyle EM, Edstedt-Bonamy A-K, Cuttini M, Toome L, et al. Specialist health care services use in a European cohort of infants born very preterm. *Dev Med Child Neurol* 2019;61:832–9. <https://doi.org/10.1111/dmcn.14112>.

- Seppänen A-V, Draper ES, Petrou S, Barros H, Andronis L, Kim SW, et al. Follow-up after very preterm birth in Europe. *Arch Dis Child Fetal Neonatal Ed* 2022a;107:113–4. <https://doi.org/10.1136/archdischild-2020-320823>.
- Seppänen A-V, Draper ES, Petrou S, Barros H, Aubert AM, Andronis L, et al. High Healthcare Use at Age 5 Years in a European Cohort of Children Born Very Preterm. *J Pediatr* 2022b;243:69-77.e9. <https://doi.org/10.1016/j.jpeds.2021.12.006>.
- Seppänen A-V, Sauvegrain P, Draper ES, Toome L, El Rafei R, Petrou S, et al. Parents' ratings of post-discharge healthcare for their children born very preterm and their suggestions for improvement: a European cohort study. *Pediatr Res* 2021;89:1004–12. <https://doi.org/10.1038/s41390-020-01120-y>.
- Serenius F, Ewald U, Farooqi A, Fellman V, Hafström M, Hellgren K, et al. Neurodevelopmental Outcomes Among Extremely Preterm Infants 6.5 Years After Active Perinatal Care in Sweden. *JAMA Pediatr* 2016;170:954–63. <https://doi.org/10.1001/jamapediatrics.2016.1210>.
- Setänen S, Lehtonen L, Parkkola R, Matomäki J, Haataja L. The motor profile of preterm infants at 11 y of age. *Pediatr Res* 2016;80:389–94. <https://doi.org/10.1038/pr.2016.90>.
- Shafie AA, Chhabra IK, Wong JHY, Mohammed NS. Mapping PedsQL™ Generic Core Scales to EQ-5D-3L utility scores in transfusion-dependent thalassemia patients. *Eur J Health Econ HEPAC Health Econ Prev Care* 2021;22:735–47. <https://doi.org/10.1007/s10198-021-01287-z>.
- Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. *Lancet Lond Engl* 2017;390:1770–80. [https://doi.org/10.1016/S0140-6736\(17\)31002-4](https://doi.org/10.1016/S0140-6736(17)31002-4).
- Shapiro BK. Cerebral palsy: A reconceptualization of the spectrum. *J Pediatr* 2004;145:S3-7. <https://doi.org/10.1016/j.jpeds.2004.05.014>.
- Smith LK, Blondel B, Van Reempts P, Draper ES, Manktelow BN, Barros H, et al. Variability in the management and outcomes of extremely preterm births across five European countries: a population-based cohort study. *Arch Dis Child Fetal Neonatal Ed* 2017;102:F400–8. <https://doi.org/10.1136/archdischild-2016-312100>.
- Smithers-Sheedy H, Badawi N, Blair E, Cans C, Himmelmann K, Krägeloh-Mann I, et al. What constitutes cerebral palsy in the twenty-first century? *Dev Med Child Neurol* 2014;56:323–8. <https://doi.org/10.1111/dmcn.12262>.
- Smits-Engelsman B. Movement Assessment Battery for Children-2, Dutch Adaptation, 2nd ed. Pearson Assessment. Amsterdam, The Netherlands: 2010.
- Smits-Engelsman B, Blank R, van der Kaay A-C, Mosterd-van der Meijjs R, Vlugt-van den Brand E, Polatajko HJ, et al. Efficacy of interventions to improve motor performance in children with developmental coordination disorder: a combined systematic review and meta-analysis. *Dev Med Child Neurol* 2013;55:229–37. <https://doi.org/10.1111/dmcn.12008>.
- Smits-Engelsman B, Schoemaker M, Delabastita T, Hoskens J, Geuze R. Diagnostic criteria for DCD: Past and future. *Hum Mov Sci* 2015;42:293–306. <https://doi.org/10.1016/j.humov.2015.03.010>.
- Solaski M, Majnemer A, Oskoui M. Contribution of socio-economic status on the prevalence of cerebral palsy: a systematic search and review. *Dev Med Child Neurol* 2014;56:1043–51. <https://doi.org/10.1111/dmcn.12456>.

- Spittle AJ, Cameron K, Doyle LW, Cheong JL, Victorian Infant Collaborative Study Group. Motor Impairment Trends in Extremely Preterm Children: 1991-2005. *Pediatrics* 2018;141. <https://doi.org/10.1542/peds.2017-3410>.
- Spittle AJ, Cheong JL, Doyle LW, Roberts G, Lee KJ, Lim J, et al. Neonatal white matter abnormality predicts childhood motor impairment in very preterm children. *Dev Med Child Neurol* 2011;53:1000–6. <https://doi.org/10.1111/j.1469-8749.2011.04095.x>.
- Spittle AJ, Dewey D, Nguyen T-N-N, Ellis R, Burnett A, Kwong A, et al. Rates of Developmental Coordination Disorder in Children Born Very Preterm. *J Pediatr* 2021;231:61-67.e2. <https://doi.org/10.1016/j.jpeds.2020.12.022>.
- Spittle AJ, Orton J. Cerebral palsy and developmental coordination disorder in children born preterm. *Semin Fetal Neonatal Med* 2014;19:84–9. <https://doi.org/10.1016/j.siny.2013.11.005>.
- Spittle AJ, Orton J, Anderson PJ, Boyd R, Doyle LW. Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. *Cochrane Database Syst Rev* 2015:CD005495. <https://doi.org/10.1002/14651858.CD005495.pub4>.
- Stahlmann N, Eisemann N, Thyen U, Herting E, Rapp M. Long-Term Health Outcomes and Health-Related Quality of Life in Adolescents from a Cohort of Extremely Premature Infants Born at Less Than 27 Weeks of Gestation in Northern Germany. *Neuropediatrics* 2016;47:388–98. <https://doi.org/10.1055/s-0036-1593373>.
- Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393. <https://doi.org/10.1136/bmj.b2393>.
- Stokes MA, Kornienko L, Scheeren AM, Koot HM, Begeer S. A comparison of children and adolescent's self-report and parental report of the PedsQL among those with and without autism spectrum disorder. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil* 2017;26:611–24. <https://doi.org/10.1007/s11136-016-1490-4>.
- Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics* 2010;126:443–56. <https://doi.org/10.1542/peds.2009-2959>.
- Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. *JAMA* 2015;314:1039–51. <https://doi.org/10.1001/jama.2015.10244>.
- Sullivan GM, Feinn R. Using Effect Size-or Why the P Value Is Not Enough. *J Grad Med Educ* 2012;4:279–82. <https://doi.org/10.4300/JGME-D-12-00156.1>.
- Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Mak Int J Soc Med Decis Mak* 2006;26:410–20. <https://doi.org/10.1177/0272989X06290495>.
- Surveillance of Cerebral Palsy in Europe. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. *Surveillance of Cerebral Palsy in Europe (SCPE). Dev Med Child Neurol* 2000;42:816–24. <https://doi.org/10.1017/s0012162200001511>.

- Taylor HG, Klein N, Drotar D, Schluchter M, Hack M. Consequences and risks of <1000-g birth weight for neuropsychological skills, achievement, and adaptive functioning. *J Dev Behav Pediatr JDBP* 2006;27:459–69. <https://doi.org/10.1097/00004703-200612000-00002>.
- Taylor HG, Minich NM, Klein N, Hack M. Longitudinal outcomes of very low birth weight: neuropsychological findings. *J Int Neuropsychol Soc JINS* 2004;10:149–63. <https://doi.org/10.1017/S1355617704102038>.
- Tran U, Gray PH, O’Callaghan MJ. Neonatal antecedents for cerebral palsy in extremely preterm babies and interaction with maternal factors. *Early Hum Dev* 2005;81:555–61. <https://doi.org/10.1016/j.earlhumdev.2004.12.009>.
- Treyvaud K, Inder TE, Lee KJ, Northam EA, Doyle LW, Anderson PJ. Can the home environment promote resilience for children born very preterm in the context of social and medical risk? *J Exp Child Psychol* 2012;112:326–37. <https://doi.org/10.1016/j.jecp.2012.02.009>.
- Tucker J, McGuire W. Epidemiology of preterm birth. *BMJ* 2004;329:675–8. <https://doi.org/10.1136/bmj.329.7467.675>.
- Twilhaar ES, de Kieviet JF, Aarnoudse-Moens CS, van Elburg RM, Oosterlaan J. Academic performance of children born preterm: a meta-analysis and meta-regression. *Arch Dis Child Fetal Neonatal Ed* 2018;103:F322–30. <https://doi.org/10.1136/archdischild-2017-312916>.
- Twilhaar ES, Pierrat V, Marchand-Martin L, Benhammou V, Kaminski M, Ancel P-Y. Profiles of Functioning in 5.5-Year-Old Very Preterm Born Children in France: The EPIPAGE-2 Study. *J Am Acad Child Adolesc Psychiatry* 2021:S0890-8567(21)01366-6. <https://doi.org/10.1016/j.jaac.2021.09.001>.
- UNESCO Institute for Statistics. International standard classification of education: ISCED 2011. Montreal, Quebec: UNESCO Institute for Statistics; 2012.
- Upton P, Lawford J, Eiser C. Parent-child agreement across child health-related quality of life instruments: a review of the literature. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil* 2008;17:895–913. <https://doi.org/10.1007/s11136-008-9350-5>.
- Uusitalo K, Haataja L, Nyman A, Ripatti L, Huhtala M, Rautava P, et al. Preterm children’s developmental coordination disorder, cognition and quality of life: a prospective cohort study. *BMJ Paediatr Open* 2020;4:e000633. <https://doi.org/10.1136/bmjpo-2019-000633>.
- 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;56:587–94. <https://doi.org/10.1111/dmcn.12295>.
- Van Hus JWP, Jeukens-Visser M, Koldewijn K, Geldof CJA, Kok JH, Nollet F, et al. Sustained developmental effects of the infant behavioral assessment and intervention program in very low birth weight infants at 5.5 years corrected age. *J Pediatr* 2013;162:1112–9. <https://doi.org/10.1016/j.jpeds.2012.11.078>.
- Varni JW, Burwinkle TM. The PedsQL as a patient-reported outcome in children and adolescents with Attention-Deficit/Hyperactivity Disorder: a population-based study. *Health Qual Life Outcomes* 2006;4:26. <https://doi.org/10.1186/1477-7525-4-26>.
- Varni JW, Burwinkle TM, Berrin SJ, Sherman SA, Artavia K, Malcarne VL, et al. The PedsQL in pediatric cerebral palsy: reliability, validity, and sensitivity of the Generic Core Scales and Cerebral Palsy Module. *Dev Med Child Neurol* 2006;48:442–9. <https://doi.org/10.1017/S001216220600096X>.

- Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr Off J Ambul Pediatr Assoc* 2003;3:329–41. [https://doi.org/10.1367/1539-4409\(2003\)003<0329:tpaapp>2.0.co;2](https://doi.org/10.1367/1539-4409(2003)003<0329:tpaapp>2.0.co;2).
- Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* 2001;39:800–12. <https://doi.org/10.1097/00005650-200108000-00006>.
- Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. *Med Care* 1999;37:126–39. <https://doi.org/10.1097/00005650-199902000-00003>.
- Vederhus BJ, Markestad T, Eide GE, Graue M, Halvorsen T. Health related quality of life after extremely preterm birth: a matched controlled cohort study. *Health Qual Life Outcomes* 2010;8:53. <https://doi.org/10.1186/1477-7525-8-53>.
- van Veen S, van Wassenaeer-Leemhuis AG, van Kaam AH, Oosterlaan J, Aarnoudse-Moens CSH. Visual perceptive skills account for very preterm children’s mathematical difficulties in preschool. *Early Hum Dev* 2019;129:11–5. <https://doi.org/10.1016/j.earlhumdev.2018.12.018>.
- Venetsanou F, Kambas A, Ellinoudis T, Fatouros I, Giannakidou D, Kourtessis T. Can the movement assessment battery for children-test be the “gold standard” for the motor assessment of children with Developmental Coordination Disorder? *Res Dev Disabil* 2011;32:1–10. <https://doi.org/10.1016/j.ridd.2010.09.006>.
- Verkerk G, Jeukens-Visser M, Koldewijn K, van Wassenaeer A, Houtzager B, Kok J, et al. Infant behavioral assessment and intervention program in very low birth weight infants improves independency in mobility at preschool age. *J Pediatr* 2011;159:933-938.e1. <https://doi.org/10.1016/j.jpeds.2011.05.035>.
- Vieira MEB, Linhares MBM. Quality of life of individuals born preterm: a systematic review of assessment approaches. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil* 2016;25:2123–39. <https://doi.org/10.1007/s11136-016-1259-9>.
- Vieira MEB, Linhares MBM. Developmental outcomes and quality of life in children born preterm at preschool- and school-age. *J Pediatr (Rio J)* 2011;87:281–91. <https://doi.org/10.2223/JPED.2096>.
- Vogels AGC, Crone MR, Hoekstra F, Reijneveld SA. Comparing three short questionnaires to detect psychosocial dysfunction among primary school children: a randomized method. *BMC Public Health* 2009;9:489. <https://doi.org/10.1186/1471-2458-9-489>.
- Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol* 2009a;8:110–24. [https://doi.org/10.1016/S1474-4422\(08\)70294-1](https://doi.org/10.1016/S1474-4422(08)70294-1).
- Volpe JJ. The encephalopathy of prematurity--brain injury and impaired brain development inextricably intertwined. *Semin Pediatr Neurol* 2009b;16:167–78. <https://doi.org/10.1016/j.spn.2009.09.005>.
- Wang CJ, McGlynn EA, Brook RH, Leonard CH, Piccuch RE, Hsueh SI, et al. Quality-of-care indicators for the neurodevelopmental follow-up of very low birth weight children: results of an expert panel process. *Pediatrics* 2006;117:2080–92. <https://doi.org/10.1542/peds.2005-1904>.

- van Wassenae-Leemhuis AG, Jeukens-Visser M, van Hus JWP, Meijssen D, Wolf M-J, Kok JH, et al. Rethinking preventive post-discharge intervention programmes for very preterm infants and their parents. *Dev Med Child Neurol* 2016;58 Suppl 4:67–73. <https://doi.org/10.1111/dmcn.13049>.
- Waters E, Davis E, Ronen GM, Rosenbaum P, Livingston M, Saigal S. Quality of life instruments for children and adolescents with neurodisabilities: how to choose the appropriate instrument. *Dev Med Child Neurol* 2009;51:660–9. <https://doi.org/10.1111/j.1469-8749.2009.03324.x>.
- Wechsler D. Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition (WPPSI-IV). Pearson. San Antonio, TX, USA: 2012.
- Wechsler D. Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III). Psychological Corporation. San Antonio, TX, USA: 2002.
- Wechsler D. Wechsler Preschool and Primary Scale of Intelligence-Revised Edition (WPPSI-R). Psychological Corporation. New York, USA: 1989.
- Wells CS, Hintze JM. Dealing with assumptions underlying statistical tests. *Psychol Sch* 2007;44:495–502. <https://doi.org/10.1002/pits.20241>.
- White H. Maximum Likelihood Estimation of Misspecified Models. *Econometrica* 1982;50:1–25. <https://doi.org/10.2307/1912526>.
- White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;30:377–99. <https://doi.org/10.1002/sim.4067>.
- Wilhelm MO. Practical Considerations for Choosing Between Tobit and SCLS or CLAD Estimators for Censored Regression Models with an Application to Charitable Giving*. *Oxf Bull Econ Stat* 2008;70:559–82. <https://doi.org/10.1111/j.1468-0084.2008.00506.x>.
- Williams J, Lee KJ, Anderson PJ. Prevalence of motor-skill impairment in preterm children who do not develop cerebral palsy: a systematic review. *Dev Med Child Neurol* 2010;52:232–7. <https://doi.org/10.1111/j.1469-8749.2009.03544.x>.
- Williams RL. A note on robust variance estimation for cluster-correlated data. *Biometrics* 2000;56:645–6. <https://doi.org/10.1111/j.0006-341x.2000.00645.x>.
- Wilson BN, Neil K, Kamps PH, Babcock S. Awareness and knowledge of developmental coordination disorder among physicians, teachers and parents. *Child Care Health Dev* 2013;39:296–300. <https://doi.org/10.1111/j.1365-2214.2012.01403.x>.
- Wilson PH, Smits-Engelsman B, Caeyenberghs K, Steenbergen B, Sugden D, Clark J, et al. Cognitive and neuroimaging findings in developmental coordination disorder: new insights from a systematic review of recent research. *Dev Med Child Neurol* 2017;59:1117–29. <https://doi.org/10.1111/dmcn.13530>.
- Wolf HT, Weber T, Schmidt S, Norman M, Varendi H, Piedvache A, et al. Mode of delivery and adverse short- and long-term outcomes in vertex-presenting very preterm born infants: a European population-based prospective cohort study. *J Perinat Med* 2021;49:923–31. <https://doi.org/10.1515/jpm-2020-0468>.
- Wolke D, Skew AJ. Bullying among siblings. *Int J Adolesc Med Health* 2012;24:17–25. <https://doi.org/10.1515/ijamh.2012.004>.
- Wong EL-Y, Cheung AW-L, Wong AY-K, Xu RH, Ramos-Goñi JM, Rivero-Arias O. Normative Profile of Health-Related Quality of Life for Hong Kong General Population Using

- Preference-Based Instrument EQ-5D-5L. *Value Health J Int Soc Pharmacoeconomics Outcomes Res* 2019;22:916–24. <https://doi.org/10.1016/j.jval.2019.02.014>.
- Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med* 2006;355:685–94. <https://doi.org/10.1056/NEJMoa053792>.
- World Health Organization. The ICD-11 classification of diseases 11th Revision 2022. <https://icd.who.int/en> (accessed August 22, 2022).
- World Health Organization. Preterm birth factsheet 2018. <https://www.who.int/news-room/fact-sheets/detail/preterm-birth> (accessed August 23, 2022).
- World Health Organization. Physical activity strategy for the WHO European Region 2016-2025. 2015.
- World Health Organization. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med* 1982 1995;41:1403–9. [https://doi.org/10.1016/0277-9536\(95\)00112-k](https://doi.org/10.1016/0277-9536(95)00112-k).
- World Health Organization. The ICD-10 classification of mental and behavioural disorders : clinical descriptions and diagnostic guidelines. Fifth Edition. World Health Organization; 1992.
- World Health Organization. International Classification of Impairments, Disabilities, and Handicaps 1980.
- World Health Organization. Constitution of the World Health Organization 1948.
- Younge N, Goldstein RF, Cotten CM, Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Survival and Neurodevelopment of Periviable Infants. *N Engl J Med* 2017;376:1890–1. <https://doi.org/10.1056/NEJMc1703379>.
- Yuksel HS, Şahin FN, Maksimovic N, Drid P, Bianco A. School-Based Intervention Programs for Preventing Obesity and Promoting Physical Activity and Fitness: A Systematic Review. *Int J Environ Res Public Health* 2020;17. <https://doi.org/10.3390/ijerph17010347>.
- Zeitlin J, Ancel P-Y, Delmas D, Bréart G, Papiernik E, EPIPAGE and MOSAIC Ile-de-France Groups. Changes in care and outcome of very preterm babies in the Parisian region between 1998 and 2003. *Arch Dis Child Fetal Neonatal Ed* 2010;95:F188-193. <https://doi.org/10.1136/adc.2008.156745>.
- Zeitlin J, Bonamy A-KE, Piedvache A, Cuttini M, Barros H, Van Reempts P, et al. Variation in term birthweight across European countries affects the prevalence of small for gestational age among very preterm infants. *Acta Paediatr Oslo Nor* 1992 2017;106:1447–55. <https://doi.org/10.1111/apa.13899>.
- Zeitlin J, Draper ES, Kollée L, Milligan D, Boerch K, Agostino R, et al. Differences in rates and short-term outcome of live births before 32 weeks of gestation in Europe in 2003: results from the MOSAIC cohort. *Pediatrics* 2008;121:e936-944. <https://doi.org/10.1542/peds.2007-1620>.
- Zeitlin J, Maier RF, Cuttini M, Aden U, Boerch K, Gadzinowski J, et al. Cohort Profile: Effective Perinatal Intensive Care in Europe (EPICE) very preterm birth cohort. *Int J Epidemiol* 2020a;49:372–86. <https://doi.org/10.1093/ije/dyz270>.

- Zeitlin J, Sentenac M, Morgan AS, Ancel PY, Barros H, Cuttini M, et al. Priorities for collaborative research using very preterm birth cohorts. *Arch Dis Child Fetal Neonatal Ed* 2020b;105:538–44. <https://doi.org/10.1136/archdischild-2019-317991>.
- 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:e366-376. <https://doi.org/10.1542/peds.2007-0169>.
- 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;39:562–80. <https://doi.org/10.1111/j.1365-2214.2012.01379.x>.
- Zwicker JG, Missiuna C, Harris SR, Boyd LA. Developmental coordination disorder: a review and update. *Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc* 2012;16:573–81. <https://doi.org/10.1016/j.ejpn.2012.05.005>.

Supplemental material

NB: The same labelling as in the published articles.

Supplemental material – Chapter 4

Supplemental Table 5. Characteristics of children followed and lost to follow-up at 5 years of age (without IPW).

Supplemental Table 6. List of variables included in the multiple imputation by chained equations and IPW programs.

Supplemental Table 7. Characteristics of children included in the study and comparison with children who had missing Movement ABC-2 scores – Sensitivity analysis without IPW.

Supplemental Table 8. Rates of movement difficulties, in total and by component (based on Movement ABC-2) – Sensitivity analysis without IPW.

Supplemental Table 9. Association between movement difficulties and sociodemographic, perinatal, and neonatal characteristics (model II) among 5-year-old children born extremely preterm – Sensitivity analysis in complete case without IPW, complete case with IPW, and multiple imputed dataset without IPW.

Supplemental Table 10. Association between movement difficulties and sociodemographic, perinatal, and neonatal characteristics (model II) among 5-year-old children born extremely preterm – Sensitivity analysis with the use of Movement ABC-2 United Kingdom norms vs Movement ABC-2 national norms.

Supplemental Information

SUPPLEMENTAL TABLE 5 Characteristics of Children Followed and Lost to Follow-Up at 5 Years of Age (Without IPW)

	Children Followed at 5 Years of Age ^a		Children Lost to Follow-Up at 5 y ^a		<i>p</i> ^b
	<i>N</i> 1021	%	<i>N</i> 633	%	
Sociodemographic characteristics					
Maternal age at childbirth, y					<.001
<25	121	11.9	151	24.0	
25–34	610	60.0	353	56.2	
≥35	286	28.1	124	19.7	
Missing	4	0.4	5	0.8	
Parity					.004
First child	604	59.9	335	53.7	
Second child	252	25.0	152	24.4	
Third child or more	153	15.2	137	22.0	
Missing	12	1.2	9	1.4	
Maternal country of birth					<.001
Native-born	786	77.2	384	65.3	
Other European country	67	6.6	51	8.7	
Non-European country	165	16.2	153	26.0	
Missing	3	0.3	45	7.1	
Perinatal and neonatal characteristics					
GA, wk					.652
≤24	132	12.9	108	17.1	
25	191	18.7	111	17.5	
26	292	28.6	183	28.9	
27	406	39.8	231	36.5	
Missing	0	0.0	0	0.0	
SGA					.021
<3rd percentile	157	15.4	73	11.5	
3rd–9th percentile	82	8.0	45	7.1	
≥10th percentile	782	76.6	515	81.4	
Missing	0	0.0	0	0.0	
Child sex					.82
Female	489	47.9	296	46.8	
Male	532	52.1	337	53.2	
Missing	0	0.0	0	0.0	
Multiple birth					.292
Singleton	733	71.8	469	74.1	
Multiple	288	28.2	164	25.9	
Missing	0	0.0	0	0.0	
Congenital anomaly					.244
No	936	91.7	583	92.1	
Yes	85	8.3	50	7.9	
Missing	0	0.0	0	0.0	
Severe neonatal morbidity ^c					.307
No	747	74.6	434	71.3	
Yes	255	25.4	175	28.7	
Missing	19	1.9	24	3.8	
BPD					.646
No	663	66.6	373	60.7	
Yes	333	33.4	241	39.3	
Missing	25	2.4	19	3.0	
Breastfeeding at discharge					<.001
No	447	44.7	341	56.7	
Yes	554	55.3	260	43.3	
Missing	20	2.0	32	5.1	

SUPPLEMENTAL TABLE 5 Continued

	Children Followed at 5 Years of Age ^a		Children Lost to Follow-Up at 5 y ^a		<i>P</i> ^b
	<i>N</i>	%	<i>N</i>	%	
Global	1021		633		
Followed-up at 2 y of age					<.001
No	175	17.1	361	57.0	
Yes	846	82.9	272	43.0	
Missing	0	0.0	0	0.0	
Country (region)					
Belgium (Flanders)	70	55.1	57	44.9	
Denmark (eastern region)	52	59.8	35	40.2	
Estonia (entire country)	38	100.0	0	0.0	
France (Burgundy, Ile-de-France, Northern Region)	189	71.6	75	28.4	
Germany (Hesse, Saarland)	79	42.7	106	57.3	
Italy (Emilia-Romagna, Lazio, Marche)	173	77.6	50	22.4	
the Netherlands (central eastern)	75	85.2	13	14.8	
Poland (Wielkopolska)	52	78.8	14	21.2	
Portugal (Lisbon, northern region)	113	72.4	43	27.6	
United Kingdom (east midlands, northern, Yorkshire, and the Humber)	138	38.7	219	61.3	
Sweden (Greater Stockholm)	42	66.7	21	33.3	

^a Values are frequencies (*N*), and % (excluding missing values) rounded to 1 decimal, all without the use of IPW to correct loss to follow-up.

^b *P* values from Wald test of logistic regressions adjusted on country.

^c Included IVH grade III or IV, cPVL, retinopathy of prematurity stage III or more, and necrotizing enterocolitis.

SUPPLEMENTAL TABLE 6 List of the Variables Included in the Multiple Imputation by Chained Equations and IPW Programs

	Perinatal or Neonatal		Sociodemographic
Previous caesarean section	Gestational age	Severe neonatal morbidity ^a	Maternal age at childbirth
Antepartum hemorrhage after wk 20	Small for gestational age	Bronchopulmonary dysplasia	Maternal country of birth
Admission for preterm labor or contractions after wk 20	Birth weight	Any surgery before discharge	Maternal parity before childbirth
The mother has preeclampsia, eclampsia, or HELLP	Apgar score <7	Use of any continuous positive airway pressure	Country
Premature rupture of membranes (>12 h)	Child sex	Use of mechanical ventilation	
Antenatal corticosteroids	Multiple pregnancy	Prophylactic surfactant in the 2 h after birth	
Delivery in maternity level 3	Hospital transfer during neonatal care	Breastfeeding at discharge	
Mode of delivery	Congenital anomalies		

HELLP syndrome, hemolysis, elevated liver enzyme, low platelets syndrome

^a Included IVH grade III or IV, cPVL, retinopathy of prematurity stage III or more, and necrotizing enterocolitis.

SUPPLEMENTAL TABLE 7 Characteristics of Children Included in the Study and Comparison With Children Who Had Missing Movement ABC-2 Scores – Sensitivity Analysis Without IPW

	Children Included in the Study ^a		Children Eligible for Inclusion but Without Movement ABC-2 ^a		<i>P</i> ^b
	N	%	N	%	
	772		119		
Sociodemographic characteristics					
Maternal age at childbirth, y					<.001
<25	89	11.6	14	11.8	
25–34	451	58.6	87	73.1	
≥35	230	29.9	18	15.1	
Missing	2	0.3	0	0.0	
Parental cohabiting status					.97
Married, couple, or cohabiting	621	85.4	101	87.1	
Single or other	106	14.6	15	12.9	
Missing	45	5.8	3	2.5	
Maternal educational level					.57
≤Lower secondary	132	17.8	19	16.7	
Upper secondary or short tertiary	319	43.0	60	52.6	
≥Bachelor	290	39.1	35	30.7	
Missing	31	4.0	5	4.2	
Household unemployment status					
Employed or other situation ^c	633	87.9	93	81.6	
At least 1 parent unemployed	87	12.1	21	18.4	
Missing	52	6.7	5	4.2	
Parity					.59
First child	464	60.8	76	64.4	
Second child	189	24.8	27	22.9	
Third child or more	110	14.4	15	12.7	
Missing	9	1.2	1	0.8	
Maternal country of birth					.82
Native-born	602	78.3	92	77.3	
Other European country	51	6.6	7	5.9	
Non-European country	116	15.1	20	16.8	
Missing	3	0.4	0	0.0	
Perinatal and neonatal characteristics					
GA, wk					.03
≤24	85	11.0	19	16.0	
25	132	17.1	27	22.7	
26	233	30.2	30	25.2	
27	322	41.7	43	36.1	
Missing	0	0.0	0	0.0	
SGA					.12
<3rd percentile	124	16.1	15	12.6	
3rd–9th percentile	67	8.7	7	5.9	
≥10th percentile	581	75.3	97	81.5	
Missing	0	0.0	0	0.0	
Child sex					.10
Female	393	50.9	51	42.9	
Male	379	49.1	68	57.1	
Missing	0	0.0	0	0.0	
Multiple birth					.88
Singleton	550	71.2	85	71.4	
Multiple	222	28.8	34	28.6	
Missing	0	0.0	0	0.0	
Congenital anomaly					.84
No	714	92.5	108	90.8	
Yes	58	7.5	11	9.2	
Missing	0	0.0	0	0.0	
Severe neonatal morbidity ^d					.07
No	607	80.2	86	73.5	
Yes	150	19.8	31	26.5	
Missing	15	1.9	2	1.7	

SUPPLEMENTAL TABLE 7 Continued

	Children Included in the Study ^a		Children Eligible for Inclusion but Without Movement ABC-2 ^a		<i>P</i> ^b
	<i>N</i>	%	<i>N</i>	%	
	772		119		
BPD					.31
No	519	69.0	82	70.1	
Yes	233	31.0	35	29.9	
Missing	20	2.6	2	1.7	
Breastfeeding at discharge					
No	311	40.9	68	59.1	
Yes	449	59.1	47	40.9	
Missing	12	1.6	4	3.4	
Characteristics of participants					
Age at assessment in years, mean (SD)	5.6	(0.3)	5.6	(0.4)	.90
Neurodevelopmental impairment ^e					.79
None	454	58.8	71	59.7	
Mild	242	31.3	36	30.3	
Moderate	76	9.8	12	10.1	
Missing	0	0.0	0	0.0	
Child development at 2 y of age ^f					
Global motor impairment ^g					.13
No	625	97.2	91	94.8	
Yes	18	2.8	5	5.2	
Missing	129	16.7	23	19.3	
Learning disability ^h					<.001
No	544	86.5	63	67.7	
Yes	85	13.5	30	32.3	
Missing	143	18.5	26	21.8	
Country (region)					
Belgium (Flanders)	48	6.2	7	5.9	
Denmark (eastern region)	40	5.2	9	7.6	
Estonia (entire country)	33	4.3	3	2.5	
France (Burgundy, Ile-de-France, northern region)	143	18.5	16	13.4	
Germany (Hesse, Saarland)	53	6.9	14	11.8	
Italy (Emilia-Romagna, Lazio, Marche)	123	15.9	28	23.5	
the Netherlands (central eastern)	69	8.9	3	2.5	
Poland (Wielkopolska)	31	4.0	11	9.2	
Portugal (Lisbon, northern region)	90	11.7	15	12.6	
United Kingdom (east midlands, northern, Yorkshire, and the Humber)	116	15.0	3	2.5	
Sweden (Greater Stockholm)	26	3.4	10	8.4	

^a Values are frequencies (*N*), % (excluding missing values) rounded to 1 decimal, and mean (SD) for continuous variables, all without the use of inverse probability weighting (IPW) to correct loss to follow-up.

^b *P* values from Wald test of logistic regressions adjusted on country.

^c Other situations included student, parental leave, home parent, and other.

^d Included IVH grade III or IV, cPVL, retinopathy of prematurity stage III or more, and necrotizing enterocolitis.

^e Combined cognitive, hearing, and visual impairment.

^f Data from the parental questionnaire filled at 2 y corrected age: 647 over 772 (83.8%) and 96 over 119 (80.7%) children have been followed at this stage.

^g Global motor impairment at 2 y of age estimated from 3 parental-reported questions on abilities on walking, sitting, and head holding.

^h Learning disability at 2 y of age estimated from the Parent Report of Children's Abilities-Revised (or the Ages and Stages Questionnaires for France only).

SUPPLEMENTAL TABLE 8 Rates of Movement Difficulties, in Total and by Component (Based on Movement ABC-2) – Sensitivity Analysis Without IPW

	Movement Difficulties ^a					
	None (>15th Percentile)		At Risk (6th–15th Percentile) ^b		Significant (≤5th Percentile)	
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%
Total ^c	366	47.4	183	23.7	223	28.9
Manual dexterity ^d	332	43.8	162	21.4	264	34.8
Aiming and catching ^d	543	71.5	72	9.5	144	19.0
Balance ^d	492	64.8	130	17.1	137	18.1

^a Values are frequencies (*N*) and % (excluding missing values) rounded to 1 decimal; both without the use of inverse probability weighting (IPW) to correct loss to follow-up.

^b As explained in the Movement ABC-2 manual,²⁴ the 16th percentile is used instead of the 15th percentile to delineate the “at risk of movement difficulties” category.

^c Total: Movement ABC-2 total score composed of the 3 components (manual dexterity, aiming and catching, and balance).

^d For the 3 component scores, the total of the *n* is not necessarily equal to 772 because mainly total scores were imputed when a test-item or a component was missing.

SUPPLEMENTAL TABLE 9 Association Between Movement Difficulties and Sociodemographic, Perinatal, and Neonatal Characteristics (Model II) Among 5-Year-Old Children Born Extremely Preterm – Sensitivity Analysis in Complete Case Without IPW, Complete Case With IPW, and Multiple Imputed Dataset Without IPW

	Complete Case Only ^c			Complete Case + IPW ^c			Multiple Imputed Dataset Only ^c		
	Movement Difficulties			Movement Difficulties			Movement Difficulties		
	At Risk RRR (95% CI)	Significant RRR (95% CI)	At Risk RRR (95% CI)	Significant RRR (95% CI)	At Risk RRR (95% CI)	Significant RRR (95% CI)	At Risk RRR (95% CI)	Significant RRR (95% CI)	
Sociodemographic characteristics									
Maternal age at childbirth, y									
<25	1.96 (0.89–4.28)	3.06 (1.40–6.67)	2.38 (1.01–5.61)	2.97 (1.30–6.76)	1.45 (0.73–2.89)	2.36 (1.18–4.74)	REF	2.36 (1.18–4.74)	REF
25–34	REF	REF	REF	REF	REF	REF	REF	REF	REF
≥35	0.66 (0.39–1.12)	1.21 (0.76–1.93)	0.69 (0.40–1.20)	1.14 (0.71–1.86)	0.66 (0.41–1.06)	1.13 (0.71–1.79)	0.66 (0.41–1.06)	1.13 (0.71–1.79)	0.66 (0.41–1.06)
Parental cohabiting status									
Married, couple, or cohabiting	REF	REF	REF	REF	REF	REF	REF	REF	REF
Single or other	1.09 (0.59–2.00)	0.89 (0.48–1.65)	1.21 (0.64–2.31)	1.01 (0.53–1.95)	1.29 (0.73–2.27)	1.02 (0.54–1.93)	1.29 (0.73–2.27)	1.02 (0.54–1.93)	1.29 (0.73–2.27)
Maternal educational level									
≤Lower secondary	1.38 (0.70–2.71)	2.75 (1.38–5.49)	1.31 (0.63–2.69)	2.89 (1.40–5.96)	1.22 (0.64–2.30)	2.18 (1.11–4.30)	1.22 (0.64–2.30)	2.18 (1.11–4.30)	1.22 (0.64–2.30)
Upper secondary or short tertiary	0.85 (0.52–1.38)	1.06 (0.65–1.75)	0.74 (0.44–1.24)	0.94 (0.55–1.59)	0.95 (0.60–1.51)	1.14 (0.69–1.89)	0.95 (0.60–1.51)	1.14 (0.69–1.89)	0.95 (0.60–1.51)
≥Bachelor	REF	REF	REF	REF	REF	REF	REF	REF	REF
Household employment status									
Employed or other situation ^b	REF	REF	REF	REF	REF	REF	REF	REF	REF
At least 1 parent unemployed	4.81 (2.51–9.22)	2.82 (1.41–5.66)	4.89 (2.45–9.77)	3.45 (1.64–7.23)	3.92 (2.17–7.10)	2.10 (1.05–4.21)	3.92 (2.17–7.10)	2.10 (1.05–4.21)	3.92 (2.17–7.10)
Parity									
Primiparous	1.54 (0.94–2.50)	1.24 (0.79–1.93)	1.65 (0.99–2.76)	1.49 (0.93–2.38)	1.39 (0.89–2.16)	1.44 (0.92–2.26)	1.39 (0.89–2.16)	1.44 (0.92–2.26)	1.39 (0.89–2.16)
Multiparous	REF	REF	REF	REF	REF	REF	REF	REF	REF
Maternal country of birth									
Native-born	REF	REF	REF	REF	REF	REF	REF	REF	REF
Other European country	0.76 (0.28–2.04)	1.59 (0.64–3.94)	0.89 (0.34–2.35)	1.58 (0.61–4.08)	0.92 (0.38–2.23)	1.49 (0.63–3.53)	0.92 (0.38–2.23)	1.49 (0.63–3.53)	0.92 (0.38–2.23)
Non-European country	0.94 (0.47–1.85)	2.52 (1.42–4.49)	0.96 (0.48–1.91)	2.51 (1.40–4.49)	0.63 (0.33–1.19)	2.08 (1.18–3.67)	0.63 (0.33–1.19)	2.08 (1.18–3.67)	0.63 (0.33–1.19)
Perinatal characteristics									
GA, wk									
≤24	1.44 (0.62–3.35)	2.10 (0.97–4.54)	1.62 (0.69–3.82)	2.45 (1.09–5.49)	1.19 (0.53–2.68)	2.06 (0.95–4.46)	1.19 (0.53–2.68)	2.06 (0.95–4.46)	1.19 (0.53–2.68)
25	0.98 (0.51–1.88)	2.23 (1.22–4.09)	1.01 (0.52–1.95)	2.34 (1.24–4.42)	1.02 (0.55–1.89)	2.19 (1.23–3.91)	1.02 (0.55–1.89)	2.19 (1.23–3.91)	1.02 (0.55–1.89)
26	0.90 (0.55–1.46)	1.43 (0.84–2.44)	1.00 (0.59–1.68)	1.44 (0.82–2.55)	1.01 (0.64–1.59)	1.43 (0.85–2.40)	1.01 (0.64–1.59)	1.43 (0.85–2.40)	1.01 (0.64–1.59)
27	REF	REF	REF	REF	REF	REF	REF	REF	REF
SGA									
<3rd percentile	1.80 (0.99–3.27)	1.20 (0.65–2.21)	1.92 (1.03–3.57)	1.22 (0.64–2.32)	1.72 (0.97–3.04)	1.48 (0.82–2.68)	1.72 (0.97–3.04)	1.48 (0.82–2.68)	1.72 (0.97–3.04)
3rd–9th percentile	0.99 (0.45–2.19)	1.40 (0.64–3.07)	1.00 (0.43–2.33)	1.54 (0.65–3.65)	0.98 (0.48–1.99)	1.46 (0.71–3.00)	0.98 (0.48–1.99)	1.46 (0.71–3.00)	0.98 (0.48–1.99)
≥10th percentile	REF	REF	REF	REF	REF	REF	REF	REF	REF
Child sex									
Female	REF	REF	REF	REF	REF	REF	REF	REF	REF
Male	1.89 (1.24–2.87)	3.14 (2.03–4.84)	1.87 (1.21–2.88)	2.85 (1.81–4.47)	1.92 (1.29–2.85)	2.74 (1.81–4.16)	1.92 (1.29–2.85)	2.74 (1.81–4.16)	1.92 (1.29–2.85)

SUPPLEMENTAL TABLE 9 Continued

	Complete Case Only ^c			Complete Case + IPW ^c			Multiple Imputed Dataset Only ^c		
	Movement Difficulties			Movement Difficulties			Movement Difficulties		
	At Risk RRR (95% CI)	Significant RRR (95% CI)		At Risk RRR (95% CI)	Significant RRR (95% CI)		At Risk RRR (95% CI)	Significant RRR (95% CI)	
Multiple birth									
Singleton	REF	REF	REF	REF	REF	REF	REF	REF	REF
Multiple	0.63 (0.40–1.00)	0.69 (0.42–1.15)	0.57 (0.36–0.91)	0.65 (0.38–1.12)	0.71 (0.46–1.09)	0.76 (0.46–1.24)			
Premature rupture of membranes									
No	REF	REF	REF	REF	REF	REF	REF	REF	REF
Yes	1.37 (0.84–2.23)	1.24 (0.78–1.97)	1.25 (0.75–2.07)	1.20 (0.74–1.95)	1.19 (0.75–1.90)	1.07 (0.66–1.74)			
Antenatal corticosteroids									
No	0.37 (0.15–0.88)	0.60 (0.26–1.39)	0.29 (0.12–0.71)	0.51 (0.22–1.19)	0.40 (0.18–0.91)	0.77 (0.33–1.75)			
Yes	REF	REF	REF	REF	REF	REF			
Congenital anomaly									
No	REF	REF	REF	REF	REF	REF	REF	REF	REF
Yes	0.59 (0.23–1.52)	1.78 (0.81–3.89)	0.48 (0.18–1.26)	1.43 (0.63–3.22)	0.87 (0.36–2.09)	2.97 (1.34–6.55)			
Neonatal characteristics									
Severe brain lesions (WH or cPVL)^d									
No	REF	REF	REF	REF	REF	REF	REF	REF	REF
Yes	1.33 (0.65–2.73)	3.35 (1.86–6.02)	1.49 (0.71–3.12)	4.18 (2.28–7.66)	1.21 (0.60–2.45)	1.82 (0.96–3.43)			
Retinopathy of prematurity									
No	REF	REF	REF	REF	REF	REF	REF	REF	REF
Yes	1.23 (0.58–2.63)	0.97 (0.49–1.91)	1.16 (0.53–2.57)	1.04 (0.51–2.12)	1.34 (0.63–2.88)	1.28 (0.65–2.50)			
Necrotizing enterocolitis									
No	REF	REF	REF	REF	REF	REF	REF	REF	REF
Yes	1.78 (0.63–4.98)	1.26 (0.47–3.39)	1.42 (0.52–3.90)	0.97 (0.36–2.59)	2.03 (0.74–5.55)	1.59 (0.57–4.46)			
BPD									
No	REF	REF	REF	REF	REF	REF	REF	REF	REF
Yes	1.75 (1.04–2.96)	2.46 (1.48–4.09)	1.73 (1.00–2.98)	2.56 (1.49–4.39)	1.83 (1.12–2.99)	2.26 (1.36–3.76)			
Postnatal corticosteroids									
No	REF	REF	REF	REF	REF	REF	REF	REF	REF
Yes	1.05 (0.61–1.81)	1.59 (0.93–2.70)	1.01 (0.58–1.76)	1.57 (0.88–2.80)	1.20 (0.71–2.01)	1.84 (1.08–3.14)			
Breastfeeding at discharge									
No	REF	REF	REF	REF	REF	REF	REF	REF	REF
Yes	1.14 (0.72–1.81)	1.20 (0.76–1.88)	1.12 (0.68–1.82)	1.26 (0.77–2.05)	1.08 (0.70–1.68)	1.06 (0.67–1.67)			
Country (region)									
Belgium (Flanders)	REF	REF	REF	REF	REF	REF	REF	REF	REF
Denmark (eastern region)	0.48 (0.18–1.32)	0.66 (0.20–2.12)	0.50 (0.18–1.38)	0.66 (0.21–2.10)	0.40 (0.15–1.07)	0.61 (0.18–2.03)			
Estonia (entire country)	0.13 (0.03–0.52)	0.67 (0.23–1.92)	0.11 (0.03–0.46)	0.67 (0.22–2.01)	0.19 (0.05–0.67)	0.85 (0.28–2.60)			
France (Burgundy, Ile-de-France, Northern Region)	0.22 (0.09–0.54)	0.24 (0.10–0.57)	0.19 (0.08–0.47)	0.26 (0.11–0.63)	0.21 (0.09–0.49)	0.17 (0.07–0.45)			
Germany (Hesse, Saarland)	0.21 (0.06–0.75)	0.53 (0.18–1.57)	0.15 (0.04–0.50)	0.57 (0.20–1.68)	0.31 (0.10–0.95)	0.58 (0.20–1.71)			

SUPPLEMENTAL TABLE 9 Continued

	Complete Case Only ^a			Complete Case + IPW ^c			Multiple Imputed Dataset Only ^c					
	Movement Difficulties			Movement Difficulties			Movement Difficulties					
	At Risk	Significant	RRR (95% CI)	At Risk	Significant	RRR (95% CI)	At Risk	Significant	RRR (95% CI)			
Italy (Emilia-Romagna, Lazio, Marche)	0.61	(0.25–1.49)	1.61	(0.71–3.66)	0.57	(0.23–1.43)	1.67	(0.71–3.92)	0.61	(0.26–1.44)	1.70	(0.70–4.14)
the Netherlands (central eastern)	0.67	(0.27–1.67)	0.26	(0.09–0.78)	0.62	(0.24–1.59)	0.28	(0.09–0.89)	0.58	(0.24–1.40)	0.24	(0.07–0.79)
Poland (Wielkopolska)	0.99	(0.20–4.81)	9.12	(2.67–31.16)	0.75	(0.15–3.81)	7.89	(2.11–29.49)	1.16	(0.23–5.99)	11.69	(2.90–47.07)
Portugal (Lisbon, northern region)	0.62	(0.25–1.55)	0.94	(0.38–2.29)	0.48	(0.19–1.23)	0.88	(0.35–2.20)	0.71	(0.29–1.72)	1.16	(0.45–3.03)
United Kingdom (east midlands, northern, Yorkshire, and the Humber)	0.67	(0.26–1.72)	3.28	(1.28–8.37)	0.50	(0.19–1.34)	3.28	(1.24–8.67)	0.72	(0.30–1.72)	2.65	(1.01–6.90)
Sweden (Greater Stockholm)	0.13	(0.03–0.64)	0.33	(0.09–1.21)	0.11	(0.02–0.56)	0.34	(0.09–1.33)	0.17	(0.04–0.75)	0.56	(0.15–2.05)

REF. reference category.

^a Values are RRR and their 95% CI from multinomial logistic regression models in complete case without IPW, complete case with IPW, and multiple imputed dataset without IPW, adjusted on sociodemographic, perinatal and neonatal factors (Model II); all taking into consideration clustering within multiple pairs, and with country modeled as a fixed effect.^b Other situations included student, parental leave, home parent, and other.^c Severe brain lesions, defined as having an IVH grade III or IV, and/or a CPVL.

SUPPLEMENTAL TABLE 10 Association Between Movement Difficulties and Sociodemographic, Perinatal, and Neonatal Characteristics (Model II)
Among 5-Year-Old Children Born Extremely Preterm – Sensitivity Analysis With the Use of Movement ABC-2 United Kingdom Norms vs Movement ABC-2 National Norms

	Movement ABC-2 United Kingdom Norms ^a				Movement ABC-2 National Norms ^a			
	Movement Difficulties				Movement Difficulties			
	At Risk		Significant		At Risk		Significant	
	RRR (95% CI)		RRR (95% CI)		RRR (95% CI)		RRR (95% CI)	
Sociodemographic characteristics								
Maternal age at childbirth, y								
<25	1.74	(0.79–3.84)	2.47	(1.15–5.30)	1.79	(0.82–3.91)	2.19	(1.06–4.52)
25–34		REF		REF		REF		REF
≥35	0.71	(0.43–1.17)	1.10	(0.67–1.80)	0.86	(0.52–1.44)	0.95	(0.59–1.54)
Parental cohabiting status								
Married, couple, or cohabiting		REF		REF		REF		REF
Single or other	1.42	(0.74–2.75)	0.91	(0.42–1.95)	1.30	(0.68–2.50)	0.91	(0.45–1.82)
Maternal educational level								
≤Lower secondary	1.21	(0.58–2.54)	2.26	(1.01–5.04)	1.08	(0.50–2.33)	1.98	(0.94–4.14)
Upper secondary short tertiary	0.87	(0.53–1.45)	1.02	(0.59–1.80)	0.95	(0.56–1.61)	0.88	(0.52–1.46)
≥Bachelor		REF		REF		REF		REF
Household employment status								
Employed or other situation ^b		REF		REF		REF		REF
At least 1 parent unemployed	3.16	(1.58–6.31)	1.96	(0.87–4.43)	2.03	(0.98–4.21)	2.07	(0.99–4.34)
Parity								
Primiparous	1.50	(0.94–2.42)	1.76	(1.07–2.91)	1.40	(0.86–2.29)	1.73	(1.08–2.76)
Multiparous		REF		REF		REF		REF
Maternal country of birth								
Native-born		REF		REF		REF		REF
Other European country	1.04	(0.44–2.43)	1.50	(0.62–3.61)	0.92	(0.39–2.17)	1.64	(0.71–3.77)
Non-European country	0.54	(0.27–1.08)	1.90	(1.04–3.46)	0.82	(0.44–1.56)	1.64	(0.92–2.91)
Perinatal characteristics								
GA, wk								
≤24	1.45	(0.62–3.44)	2.30	(1.03–5.13)	1.67	(0.67–4.16)	2.35	(1.08–5.11)
25	1.10	(0.59–2.07)	2.42	(1.31–4.48)	1.24	(0.66–2.33)	2.02	(1.13–3.62)
26	1.17	(0.71–1.93)	1.34	(0.76–2.36)	1.27	(0.76–2.11)	1.21	(0.71–2.06)
27		REF		REF		REF		REF
SGA								
<3rd percentile	1.82	(1.00–3.30)	1.59	(0.83–3.04)	1.99	(1.09–3.66)	1.38	(0.76–2.52)
3rd–9th percentile	1.02	(0.47–2.18)	1.58	(0.73–3.40)	1.16	(0.52–2.59)	1.80	(0.88–3.71)
≥10th percentile		REF		REF		REF		REF
Child sex								
Female		REF		REF		REF		REF
Male	1.81	(1.18–2.76)	2.23	(1.42–3.51)	1.78	(1.15–2.77)	2.08	(1.36–3.18)
Multiple birth								
Singleton		REF		REF		REF		REF
Multiple	0.65	(0.42–1.01)	0.78	(0.46–1.33)	0.65	(0.41–1.02)	0.81	(0.49–1.32)
Premature rupture of membranes								
No		REF		REF		REF		REF
Yes	1.14	(0.69–1.88)	1.04	(0.62–1.72)	1.29	(0.78–2.13)	1.18	(0.72–1.93)
Antenatal corticosteroids								
No	0.35	(0.15–0.81)	0.80	(0.33–1.96)	0.42	(0.18–1.01)	0.87	(0.39–1.95)
Yes		REF		REF		REF		REF
Congenital anomaly								
No		REF		REF		REF		REF
Yes	0.69	(0.27–1.76)	2.33	(0.95–5.72)	0.83	(0.29–2.38)	2.15	(0.90–5.13)
Neonatal characteristics								
Severe brain lesions (IVH or cPVL) ^c								
No		REF		REF		REF		REF
Yes	1.31	(0.63–2.73)	2.17	(1.14–4.12)	1.69	(0.80–3.61)	2.24	(1.19–4.22)
Retinopathy of prematurity								
No		REF		REF		REF		REF
Yes	1.21	(0.53–2.75)	1.34	(0.66–2.76)	1.35	(0.60–3.05)	1.43	(0.70–2.92)

SUPPLEMENTAL TABLE 10 Continued

	Movement ABC-2 United Kingdom Norms ^a				Movement ABC-2 National Norms ^a			
	Movement Difficulties				Movement Difficulties			
	At Risk		Significant		At Risk		Significant	
	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
Necrotizing enterocolitis								
No		REF		REF		REF		REF
Yes	1.54	(0.57–4.19)	1.10	(0.41–2.96)	2.20	(0.77–6.29)	1.11	(0.42–2.97)
BPD								
No		REF		REF		REF		REF
Yes	1.94	(1.13–3.33)	2.54	(1.47–4.40)	1.42	(0.80–2.52)	2.46	(1.48–4.09)
Postnatal corticosteroids								
No		REF		REF		REF		REF
Yes	1.05	(0.61–1.82)	1.94	(1.09–3.44)	0.86	(0.49–1.50)	1.81	(1.08–3.04)
Breastfeeding at discharge								
No	1.01	(0.62–1.64)	0.98	(0.59–1.62)	0.84	(0.51–1.38)	1.00	(0.62–1.61)
Yes		REF		REF		REF		REF
Country (region)								
Belgium (Flanders)		REF		REF		REF		REF
Denmark (eastern region)	0.42	(0.15–1.19)	0.66	(0.20–2.21)	0.65	(0.22–1.86)	0.37	(0.12–1.18)
Estonia (entire country)	0.16	(0.04–0.59)	0.85	(0.26–2.82)	0.26	(0.07–0.99)	0.45	(0.14–1.44)
France (Burgundy, Ile-de-France, northern region)	0.19	(0.08–0.47)	0.20	(0.07–0.54)	0.38	(0.15–0.94)	0.24	(0.10–0.59)
Germany (Hesse, Saarland)	0.24	(0.08–0.72)	0.64	(0.21–1.97)	0.45	(0.15–1.40)	0.37	(0.13–1.11)
Italy (Emilia-Romagna, Lazio, Marche)	0.56	(0.23–1.35)	1.80	(0.70–4.64)	0.31	(0.12–0.82)	0.48	(0.19–1.19)
the Netherlands (central eastern)	0.52	(0.21–1.29)	0.26	(0.08–0.88)	0.66	(0.23–1.88)	0.90	(0.34–2.36)
Poland (Wielkopolska)	0.81	(0.15–4.35)	9.61	(2.09–44.17)	1.38	(0.26–7.44)	5.42	(1.25–23.38)
Portugal (Lisbon, northern region)	0.55	(0.22–1.37)	1.15	(0.42–3.17)	0.96	(0.37–2.48)	0.65	(0.25–1.71)
United Kingdom (east midlands, northern, Yorkshire, and the Humber)	0.53	(0.22–1.32)	2.46	(0.87–6.92)	0.97	(0.37–2.52)	1.36	(0.52–3.54)
Sweden (Greater Stockholm)	0.14	(0.03–0.67)	0.61	(0.15–2.44)	0.31	(0.07–1.35)	0.33	(0.08–1.29)

REF, reference category.

^a Values are RRR and their 95% CI from multinomial logistic regression models with Movement ABC-2 United Kingdom norms (left columns) and Movement ABC-2 national norms (right columns): adjusted on sociodemographic, perinatal and neonatal factors (Model II); both taking into consideration clustering within multiple pairs, with country modeled as a fixed effect, and with the use of IPW and multiple imputed dataset.

^b Other situations included student, parental leave, home parent, and other.

^c Severe brain lesions, defined as having an IVH grade III or IV, and/or a cPVL.

Supplemental material – Chapter 5

Supplemental Table 1. Characteristics of children followed and lost to follow-up at 5 years of age (without IPW).

Supplemental Table 2. List of variables included in the multiple imputation by chained equations and IPW programs.

Supplemental Table 3. Association of sociodemographic, perinatal and neonatal factors with risks of non-CP MD and CP (model 3) – Sensitivity analysis in complete case without IPW, complete case with IPW, and multiple imputed dataset without IPW.

Supplemental Table 4. Association of sociodemographic, perinatal and neonatal factors with risks of non-CP MD and CP – Sensitivity analysis with the exclusion of children with severe NDI (n=20) in the CP group.

Supplemental Table 1. Characteristics of children followed and lost to follow-up at 5 years of age (without IPW).

	Children followed at 5 years of age		Children lost to follow-up at 5 years		<i>p-value</i> ^a
	N	%	N	%	
	1,021		633		
Sociodemographic characteristics					
Maternal age at childbirth (years)					<0.001
<25	121	11.9	151	24.0	
25-34	610	60.0	353	56.2	
≥35	286	28.1	124	19.7	
<i>Missing</i>	4	0.4	5	0.8	
Parity					0.010
First child	604	59.9	335	53.7	
Second child	252	25.0	152	24.4	
Third child or more	153	15.2	137	22.0	
<i>Missing</i>	12	1.2	9	1.4	
Maternal country of birth					<0.001
Native-born	786	77.2	384	65.3	
Other European country	67	6.6	51	8.7	
Non-European country	165	16.2	153	26.0	
<i>Missing</i>	3	0.3	45	7.1	
Perinatal and neonatal characteristics					
Gestational age (completed weeks)					0.69
≤24	132	12.9	108	17.1	
25	191	18.7	111	17.5	
26	292	28.6	183	28.9	
27	406	39.8	231	36.5	
<i>Missing</i>	0	0.0	0	0.0	
Small for gestational age					0.031
<3 rd percentile	157	15.4	73	11.5	
3-9 th percentile	82	8.0	45	7.1	
≥10 th percentile	782	76.6	515	81.4	
<i>Missing</i>	0	0.0	0	0.0	
Child sex					0.83
Female	489	47.9	296	46.8	
Male	532	52.1	337	53.2	
<i>Missing</i>	0	0.0	0	0.0	
Multiple birth					0.41
Singleton	733	71.8	469	74.1	
Multiple	288	28.2	164	25.9	
<i>Missing</i>	0	0.0	0	0.0	
Congenital anomaly					0.23
No	936	91.7	583	92.1	
Yes	85	8.3	50	7.9	
<i>Missing</i>	0	0.0	0	0.0	
Severe neonatal morbidity^b					0.31
No	747	74.6	434	71.3	
Yes	255	25.4	175	28.7	
<i>Missing</i>	19	1.9	24	3.8	
Bronchopulmonary dysplasia^c					0.54
No	642	63.9	366	59.2	
Yes	362	36.1	252	40.8	
<i>Missing</i>	17	1.7	15	2.4	
Breastfeeding at discharge					<0.001
No	447	44.7	341	56.7	
Yes	554	55.3	260	43.3	
<i>Missing</i>	20	2.0	32	5.1	

Supplemental Table 1. Continued.

	Children followed at 5 years of age		Children lost to follow-up at 5 years		<i>p-value</i> ^a
	N	%	N	%	
	1,021		633		
Global					
Followed-up at 2 years of age					<i><0.001</i>
No	175	17.1	361	57.0	
Yes	846	82.9	272	43.0	
Missing	0	0.0	0	0.0	
Country (region)					
Belgium (Flanders)	70	55.1	57	44.9	
Denmark (Eastern Region)	52	59.8	35	40.2	
Estonia (entire country)	38	100.0	0	0.0	
France (Burgundy, Ile-de-France, Northern Region)	189	71.6	75	28.4	
Germany (Hesse, Saarland)	79	42.7	106	57.3	
Italy (Emilia-Romagna, Lazio, Marche)	173	77.6	50	22.4	
The Netherlands (Central Eastern)	75	85.2	13	14.8	
Poland (Wielkopolska)	52	78.8	14	21.2	
Portugal (Lisbon, Northern Region)	113	72.4	43	27.6	
The United Kingdom (East Midlands, Northern, Yorkshire and the Humber)	138	38.7	219	61.3	
Sweden (Greater Stockholm)	42	66.7	21	33.3	

Abbreviations: IPW, inverse probability weighting.

Values are frequencies (Ns rounded to a whole number) and percentages (% excluding missing values and rounded to one decimal), all without the use of inverse probability weighting (IPW).

^aP-values from Wald test of logistic regressions adjusted on country and taking into consideration clustering within multiple pairs.

^bIncluded intraventricular hemorrhage grade III/IV, cystic periventricular leukomalacia, retinopathy of prematurity stage III or more, and surgical necrotizing enterocolitis.

^cDefined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.

Supplemental Table 2. List of the variables included in the multiple imputation by chained equations and IPW programs.

	Perinatal/Neonatal		Sociodemographic
Previous caesarean section	Gestational age	Severe neonatal morbidity ^a	Maternal age at childbirth
Antepartum hemorrhage after week 20	Small for gestational age	Bronchopulmonary dysplasia ^b	Maternal country of birth
Admission for preterm labor/contractions after week 20	Birthweight	Any surgery before discharge	Maternal parity before childbirth
The mother has preeclampsia/eclampsia/HELLP	Apgar score <7	Use of any continuous positive airway pressure	Country
Premature rupture of membranes (>12hours)	Child sex	Use of mechanical ventilation	
Antenatal corticosteroids	Multiple pregnancy	Prophylactic surfactant in the 2 hours after birth	
Delivery in a level 3 maternity unit	Hospital transfer during neonatal care	Breastfeeding at discharge	
Mode of delivery	Congenital anomalies		

Abbreviations: IPW, inverse probability weighting. HELLP syndrome, Hemolysis, Elevated Liver enzyme, Low Platelets syndrome.

^aIncluded intraventricular hemorrhage grade III/IV, cystic periventricular leukomalacia, retinopathy of prematurity stage III or more, and surgical necrotizing enterocolitis.

^bDefined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.

Supplemental Table 3. Association of sociodemographic, perinatal and neonatal factors with risks of non-CP MD and CP (model 3) – Sensitivity analysis in complete case without IPW, complete case with IPW, and multiple imputed dataset without IPW.

	Complete case only		Complete case with IPW		Multiple imputed dataset without IPW	
	Non-CP MD RRR [95% CI]	CP RRR [95% CI]	Non-CP MD RRR [95% CI]	CP RRR [95% CI]	Non-CP MD RRR [95% CI]	CP RRR [95% CI]
Sociodemographic factors						
Maternal age at childbirth (years) [25-34 years]						
<25	2.36 [1.02-5.47]	2.09 [0.76-5.73]	2.21 [0.92-5.28]	2.66 [0.96-7.35]	2.23 [1.14-4.39]	1.70 [0.77-3.75]
≥35	0.99 [0.59-1.66]	0.53 [0.25-1.15]	0.96 [0.56-1.66]	0.46 [0.20-1.05]	1.05 [0.66-1.66]	0.67 [0.35-1.26]
Parental cohabiting status [Married/Couple/Cohabiting]						
Single/Other	0.76 [0.36-1.59]	1.33 [0.63-2.82]	0.76 [0.35-1.64]	1.75 [0.80-3.81]	1.18 [0.62-2.25]	1.22 [0.61-2.42]
Maternal educational level [High education ISCED 6-8]						
Low education ISCED 0-2	2.89 [1.42-5.91]	1.25 [0.40-3.84]	2.74 [1.26-5.92]	1.36 [0.44-4.23]	2.58 [1.38-4.81]	1.42 [0.58-3.44]
Intermediate education ISCED 3-5	1.01 [0.58-1.74]	1.06 [0.52-2.15]	0.86 [0.48-1.53]	0.95 [0.46-1.96]	1.10 [0.67-1.81]	0.98 [0.54-1.79]
Household employment status [Parents employed]						
At least one parent unemployed	3.33 [1.59-7.00]	2.38 [0.93-6.11]	3.82 [1.74-8.39]	2.10 [0.78-5.67]	2.52 [1.25-5.09]	2.24 [0.97-5.16]
Parity [Multiparous]						
Primiparous	1.39 [0.85-2.29]	0.72 [0.38-1.36]	1.71 [1.02-2.86]	0.77 [0.38-1.54]	1.28 [0.83-1.98]	0.75 [0.43-1.30]
Maternal country of birth [Native-born]						
Other European country	2.18 [0.79-6.04]	1.81 [0.52-6.34]	2.41 [0.82-7.10]	1.75 [0.48-6.41]	1.34 [0.60-2.97]	0.74 [0.22-2.48]
Non-European country	2.50 [1.30-4.80]	1.31 [0.54-3.16]	2.37 [1.19-4.69]	1.16 [0.50-2.73]	1.88 [1.07-3.31]	1.33 [0.70-2.55]

Supplemental Table 3. Continued.

	Complete case only			Complete case with IPW			Multiple imputed dataset without IPW		
	Non-CP MD RRR [95% CI]	CP RRR [95% CI]		Non-CP MD RRR [95% CI]	CP RRR [95% CI]		Non-CP MD RRR [95% CI]	CP RRR [95% CI]	
Perinatal factors									
GA (weeks) [27 weeks]									
≤24	3.59 [1.57-8.19]	2.20 [0.76-6.34]		4.94 [2.00-12.22]	2.28 [0.71-7.31]		3.08 [1.59-5.97]	2.24 [0.98-5.10]	
25	3.01 [1.56-5.82]	3.52 [1.61-7.68]		3.84 [1.88-7.83]	3.09 [1.38-6.89]		2.87 [1.63-5.04]	2.98 [1.52-5.85]	
26	2.09 [1.14-3.82]	1.04 [0.46-2.35]		2.33 [1.23-4.43]	1.00 [0.44-2.27]		1.75 [1.04-2.93]	1.28 [0.66-2.47]	
SGA [≥10th percentile]									
<3 rd percentile	1.68 [0.82-3.45]	1.07 [0.32-3.57]		2.03 [0.94-4.36]	0.97 [0.28-3.32]		1.68 [0.90-3.12]	1.30 [0.50-3.38]	
3 rd -9 th percentile	1.42 [0.57-3.52]	1.45 [0.47-4.45]		1.84 [0.69-4.90]	1.39 [0.42-4.56]		1.35 [0.63-2.89]	1.12 [0.43-2.95]	
Apgar <7 [No]									
Yes	1.50 [0.86-2.63]	1.71 [0.87-3.37]		1.39 [0.78-2.49]	2.02 [1.01-4.01]		1.53 [0.92-2.54]	2.21 [1.25-3.91]	
Child sex [Female]									
Male	3.34 [2.02-5.53]	2.84 [1.55-5.18]		3.20 [1.84-5.55]	2.28 [1.21-4.31]		2.99 [1.97-4.53]	3.55 [2.10-5.99]	
Multiple birth [Singleton]									
Multiple	0.80 [0.45-1.42]	1.05 [0.49-2.23]		0.80 [0.44-1.46]	0.92 [0.43-1.95]		0.88 [0.55-1.41]	1.07 [0.60-1.92]	
Delivery in a level 3 maternity unit [Yes]									
No	0.47 [0.19-1.13]	0.76 [0.31-1.86]		0.54 [0.21-1.38]	0.91 [0.37-2.19]		0.81 [0.40-1.62]	1.31 [0.59-2.92]	
Antepartum hemorrhage after week 20 [No]									
Yes	1.45 [0.84-2.50]	1.29 [0.65-2.56]		1.55 [0.87-2.78]	1.29 [0.63-2.63]		1.34 [0.83-2.18]	1.35 [0.75-2.42]	
PROM [No]									
Yes	1.15 [0.67-1.98]	0.90 [0.40-2.04]		1.11 [0.62-1.99]	0.99 [0.41-2.36]		0.99 [0.61-1.61]	0.89 [0.47-1.69]	
Preeclampsia/eclampsia/HELLP [No]									
Yes	1.51 [0.66-3.45]	0.83 [0.23-3.02]		1.40 [0.59-3.33]	0.83 [0.22-3.08]		1.51 [0.72-3.14]	1.09 [0.38-3.13]	
Antenatal corticosteroids [Yes]									
No	0.44 [0.15-1.29]	1.47 [0.59-3.65]		0.37 [0.12-1.12]	1.07 [0.42-2.73]		0.70 [0.32-1.54]	1.40 [0.66-2.97]	
Congenital anomaly [No]									
Yes	1.90 [0.90-4.00]	3.30 [1.29-8.45]		1.35 [0.62-2.92]	3.63 [1.33-9.92]		2.44 [1.18-5.06]	2.91 [1.19-7.10]	

Supplemental Table 3. Continued.

	Complete case only			Complete case with IPW			Multiple imputed dataset without IPW		
	Non-CP MD RRR [95% CI]	CP RRR [95% CI]		Non-CP MD RRR [95% CI]	CP RRR [95% CI]		Non-CP MD RRR [95% CI]	CP RRR [95% CI]	
Neonatal factors									
IVH grades [None]									
Grade I/II	1.65 [0.92-2.94]	2.74 [1.20-6.28]		1.75 [0.96-3.18]	3.26 [1.42-7.47]		1.50 [0.94-2.40]	2.70 [1.36-5.39]	
Grade III	0.81 [0.30-2.17]	6.41 [2.30-17.86]		0.89 [0.34-2.37]	8.09 [2.93-22.32]		1.14 [0.44-3.01]	9.21 [3.49-24.32]	
Grade IV	5.02 [1.47-17.09]	48.69 [12.65-187.41]		8.12 [2.26-29.17]	55.57 [13.60-227.02]		6.34 [1.87-21.51]	61.75 [16.50-231.08]	
cPVL [No]									
Yes	3.01 [1.12-8.08]	23.13 [8.19-65.32]		4.06 [1.46-11.26]	27.73 [10.01-76.86]		2.08 [0.92-4.71]	16.17 [7.00-37.33]	
ROP [No]									
Yes	1.45 [0.67-3.11]	3.00 [1.11-8.09]		1.69 [0.75-3.83]	2.89 [1.01-8.29]		1.63 [0.86-3.10]	2.43 [1.06-5.59]	
NEC [No]									
Yes	1.36 [0.48-3.84]	2.70 [0.83-8.75]		1.02 [0.37-2.85]	2.17 [0.60-7.81]		1.72 [0.67-4.45]	3.95 [1.40-11.16]	
BPD^a [No]									
Yes	2.65 [1.52-4.62]	3.85 [1.88-7.91]		2.83 [1.60-5.00]	3.48 [1.67-7.26]		2.25 [1.40-3.62]	3.31 [1.84-5.93]	
Postnatal corticosteroids [No]									
Yes	2.46 [1.36-4.45]	3.73 [1.83-7.60]		2.72 [1.43-5.17]	3.16 [1.48-6.73]		2.12 [1.30-3.46]	2.61 [1.49-4.58]	
Confirmed late infection [No]									
Yes	1.40 [0.84-2.35]	2.11 [1.02-4.34]		1.34 [0.78-2.30]	1.97 [0.94-4.15]		1.24 [0.80-1.93]	2.49 [1.39-4.45]	

Abbreviations: CP, cerebral palsy; MD, movement difficulties; IPW, inverse probability weighting; RRR, relative risk ratio; CI, confidence interval; ISCED, International Standard Classification of Education;³⁹ GA, gestational age; SGA, small for gestational age; PROM, premature rupture of membranes; HELLP, hemolysis, elevated liver enzymes, and low platelets (syndrome); IVH, intraventricular hemorrhage; cPVL, cystic periventricular leukomalacia; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia.

Values are relative risk ratios and their 95% confidence intervals (RRR [95% CI]) of having non-CP MD or CP compared to children without MD using multinomial logistic regression models in complete case without inverse probability weighting (IPW), complete case with IPW, and multiple imputed dataset without IPW; all adjusted for all sociodemographic and perinatal factors (model 3), taking into consideration clustering within multiple pairs, and with country modelled as a fixed effect.

^aDefined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.

Supplemental Table 4. Association of sociodemographic, perinatal and neonatal factors with risks of non-CP MD and CP – Sensitivity analysis with exclusion of children with severe NDI (n=20) in the CP group.

	Non-cerebral palsy movement difficulties						Cerebral palsy									
	Adjusted for all sociodemographic factors		Adjusted for all sociodemographic and perinatal factors		Adjusted for all sociodemographic, perinatal and neonatal factors		Adjusted for all sociodemographic factors		Adjusted for all sociodemographic and perinatal factors		Adjusted for all sociodemographic, perinatal and neonatal factors					
	Unadjusted	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]					
Sociodemographic factors																
Maternal age at childbirth (years) [25-34 years]																
<25	2.92	[1.46-5.82]	2.38	[1.16-4.90]	2.49	[1.18-5.28]	2.95	[1.30-6.71]	1.79	[0.68-4.68]	1.70	[0.68-4.24]	1.42	[0.59-3.42]	1.74	[0.70-4.35]
≥35	0.97	[0.63-1.50]	1.06	[0.67-1.69]	1.09	[0.66-1.80]	1.08	[0.64-1.83]	0.73	[0.39-1.38]	0.64	[0.32-1.27]	0.70	[0.34-1.46]	0.80	[0.34-1.87]
Parental cohabiting status [Married/Couple/Cohabiting]																
Single/Other	1.06	[0.53-2.09]	1.02	[0.49-2.13]	1.20	[0.54-2.69]	1.19	[0.54-2.63]	0.91	[0.42-1.96]	0.89	[0.40-1.97]	0.87	[0.39-1.95]	0.83	[0.35-1.99]
Maternal educational level [High education ISCED 6-8]																
Low education ISCED 0-2	2.82	[1.56-5.10]	2.29	[1.13-4.63]	2.50	[1.15-5.41]	2.10	[0.96-4.61]	1.66	[0.74-3.73]	1.36	[0.56-3.29]	1.23	[0.46-3.28]	0.92	[0.33-2.60]
Intermediate education ISCED 3-5	1.16	[0.73-1.86]	1.00	[0.58-1.72]	1.08	[0.60-1.94]	0.91	[0.50-1.66]	0.98	[0.54-1.79]	0.79	[0.41-1.53]	0.86	[0.43-1.70]	0.64	[0.28-1.44]
Household employment status [Parents employed]																
At least one parent unemployed	2.30	[1.05-5.01]	2.25	[1.08-4.71]	2.07	[0.87-4.93]	2.27	[0.92-5.59]	2.74	[1.14-6.57]	2.54	[1.12-5.75]	1.41	[0.56-3.55]	1.66	[0.63-4.37]
Parity [Multiparous]																
Primiparous	1.46	[0.95-2.22]	1.59	[1.01-2.48]	1.58	[0.99-2.54]	1.52	[0.91-2.53]	0.62	[0.36-1.09]	0.62	[0.35-1.09]	0.67	[0.36-1.23]	0.53	[0.27-1.03]
Maternal country of birth [Native-born]																
Other European country	1.40	[0.66-2.97]	1.22	[0.58-2.57]	1.35	[0.58-3.16]	1.37	[0.56-3.31]	1.12	[0.35-3.58]	0.86	[0.28-2.59]	0.94	[0.30-2.95]	0.84	[0.27-2.60]
Non-European country	1.43	[0.78-2.64]	1.35	[0.73-2.51]	1.60	[0.85-3.01]	1.90	[1.00-3.59]	1.48	[0.69-3.19]	1.21	[0.61-2.39]	1.37	[0.68-2.74]	1.93	[0.88-4.23]

Supplemental Table 4. Continued.

		Non-cerebral palsy movement difficulties				Cerebral palsy			
		Adjusted for all sociodemographic and perinatal factors	Adjusted for all sociodemographic and perinatal factors	Adjusted for all sociodemographic, perinatal and neonatal factors	Unadjusted	Adjusted for all sociodemographic factors	Adjusted for all sociodemographic and perinatal factors	Adjusted for all sociodemographic, perinatal and neonatal factors	
		RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	
Perinatal factors									
GA (weeks) [27 weeks]									
≤24		3.75 [1.98-7.09]	3.96 [2.09-7.50]	4.44 [2.18-9.03]	2.26 [1.02-4.98]	1.58 [0.57-4.39]	1.81 [0.65-5.06]	0.80 [0.21-3.09]	
25		2.43 [1.39-4.25]	3.33 [1.90-5.86]	3.56 [1.94-6.51]	2.29 [1.18-4.44]	2.07 [1.01-4.23]	2.71 [1.33-5.54]	1.51 [0.68-3.35]	
26		1.27 [0.77-2.12]	1.64 [0.94-2.84]	1.74 [0.98-3.08]	1.40 [0.77-2.53]	0.66 [0.32-1.35]	0.85 [0.41-1.77]	0.78 [0.34-1.77]	
SGA [≥10th percentile]									
<3 rd percentile		1.89 [1.12-3.21]	1.82 [1.07-3.09]	1.99 [1.03-3.88]	1.45 [0.73-2.89]	1.06 [0.47-2.38]	1.77 [0.63-5.00]	1.84 [0.63-5.41]	
3 rd -9 th percentile		1.09 [0.56-2.13]	1.24 [0.62-2.49]	1.52 [0.68-3.39]	1.44 [0.62-3.32]	0.88 [0.32-2.39]	1.49 [0.51-4.32]	1.36 [0.41-4.52]	
Apgar <7 [No]		1.50 [0.89-2.56]	1.49 [0.89-2.49]	1.31 [0.76-2.26]	1.08 [0.62-1.89]	3.33 [1.73-6.41]	2.35 [1.25-4.43]	2.05 [1.00-4.20]	
Yes									
Child sex [Female]		2.38 [1.56-3.62]	2.30 [1.49-3.56]	2.48 [1.57-3.93]	2.23 [1.39-3.59]	2.87 [1.67-4.95]	2.84 [1.60-5.04]	3.76 [1.96-7.22]	
Male									
Multiple birth [Singleton]		0.59 [0.37-0.94]	0.69 [0.44-1.10]	0.89 [0.54-1.46]	0.87 [0.50-1.50]	0.65 [0.35-1.20]	0.97 [0.51-1.86]	0.72 [0.34-1.51]	
Multiple									
Delivery in a level 3 maternity unit [Yes]		1.04 [0.58-1.87]	0.91 [0.49-1.71]	1.01 [0.49-2.08]	0.93 [0.45-1.90]	2.51 [1.19-5.29]	1.48 [0.65-3.36]	1.42 [0.62-3.26]	
No									
Antepartum hemorrhage after week 20 [No]		1.43 [0.87-2.34]	1.41 [0.85-2.36]	1.21 [0.69-2.10]	1.30 [0.73-2.33]	1.65 [0.85-3.22]	1.24 [0.63-2.44]	0.68 [0.29-1.63]	
Yes									
PROM [No]		1.00 [0.62-1.60]	1.06 [0.65-1.74]	0.96 [0.55-1.65]	0.86 [0.49-1.49]	0.86 [0.45-1.64]	0.94 [0.47-1.91]	0.67 [0.31-1.46]	
Yes									
Preeclampsia/eclampsia/HELLP [No]		1.51 [0.84-2.70]	1.55 [0.84-2.87]	1.37 [0.64-2.93]	1.04 [0.44-2.45]	0.86 [0.35-2.12]	0.98 [0.31-3.10]	0.60 [0.16-2.22]	
Yes									
Antenatal corticosteroids [Yes]		0.76 [0.36-1.61]	0.63 [0.30-1.31]	0.72 [0.30-1.70]	0.59 [0.25-1.44]	2.52 [1.24-5.11]	2.15 [1.00-4.61]	1.41 [0.58-3.42]	
No									
Congenital anomaly [No]		1.99 [0.87-4.56]	1.79 [0.81-3.98]	1.82 [0.76-4.35]	1.82 [0.72-4.64]	1.69 [0.65-4.38]	1.99 [0.68-5.83]	1.26 [0.40-3.95]	
Yes									

Supplemental Table 4. Continued.

	Non-cerebral palsy movement difficulties				Cerebral palsy			
	Adjusted for all sociodemographic and perinatal factors		Adjusted for all sociodemographic, perinatal and neonatal factors		Adjusted for all sociodemographic factors		Adjusted for all sociodemographic and perinatal factors	
	Unadjusted	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]	Unadjusted	RRR [95% CI]	RRR [95% CI]	RRR [95% CI]
Neonatal factors								
IVH grades [None]								
Grade I/II	1.80 [1.14-2.83]	1.83 [1.16-2.89]	1.47 [0.91-2.37]	1.41 [0.86-2.30]	2.17 [1.10-4.27]	2.89 [1.39-6.02]	2.47 [1.09-5.62]	2.21 [0.98-4.99]
Grade III	1.98 [0.82-4.76]	2.03 [0.82-5.00]	1.36 [0.56-3.26]	1.30 [0.54-3.11]	8.35 [3.18-21.88]	11.58 [4.35-30.87]	9.63 [3.38-27.44]	8.72 [3.04-25.00]
Grade IV	10.28 [2.76-38.25]	11.16 [3.17-39.29]	8.14 [2.33-28.35]	8.26 [1.75-39.03]	106.46 [23.50-482.24]	107.53 [25.71-449.70]	92.39 [21.96-388.69]	78.64 [11.11-556.78]
cPVL [No]								
Yes	2.47 [1.00-6.08]	2.49 [1.07-5.82]	2.46 [1.07-5.61]	2.43 [1.03-5.72]	15.41 [5.58-42.55]	16.08 [6.02-42.96]	21.18 [8.38-53.56]	14.87 [4.44-49.81]
ROP [No]								
Yes	3.51 [1.83-6.72]	2.86 [1.51-5.39]	1.93 [0.98-3.80]	1.38 [0.69-2.75]	3.01 [1.29-7.01]	2.69 [1.14-6.35]	1.91 [0.72-5.09]	1.55 [0.51-4.71]
NEC [No]								
Yes	1.21 [0.36-4.00]	1.18 [0.40-3.44]	1.27 [0.50-3.22]	1.21 [0.46-3.20]	6.97 [2.02-24.03]	5.63 [1.77-17.86]	5.95 [1.91-18.58]	3.70 [0.90-15.12]
BPD^a [No]								
Yes	3.25 [2.09-5.07]	3.90 [2.46-6.17]	2.74 [1.63-4.62]	2.43 [1.40-4.23]	2.41 [1.32-4.39]	2.65 [1.48-4.74]	2.01 [1.04-3.87]	1.90 [0.85-4.23]
Postnatal corticosteroids [No]								
Yes	3.24 [2.05-5.13]	3.35 [2.05-5.47]	2.40 [1.41-4.09]	1.85 [1.05-3.24]	1.74 [0.96-3.16]	1.99 [1.13-3.50]	1.69 [0.90-3.18]	1.35 [0.68-2.67]
Confirmed late infection [No]								
Yes	1.45 [0.95-2.20]	1.41 [0.92-2.16]	1.04 [0.63-1.71]	0.91 [0.54-1.55]	2.52 [1.33-4.77]	2.47 [1.34-4.55]	2.06 [1.07-3.98]	1.88 [0.92-3.84]

Abbreviations: CP, cerebral palsy. MD, movement difficulties. NDI, neurodevelopmental impairment. RRR, relative risk ratio. CI, confidence interval. ISCED, International Standard Classification of Education.³⁹ GA, gestational age. SGA, small for gestational age. PROM, premature rupture of membranes. HELLP, hemolysis, elevated liver enzymes, and low platelets (syndrome). IVH, intraventricular hemorrhage. cPVL, cystic periventricular leukomalacia. ROP, retinopathy of prematurity. NEC, necrotizing enterocolitis. BPD, bronchopulmonary dysplasia.

Values are relative risk ratios and their 95% confidence intervals (RRR [95% CI]) of having non-CP MD or CP compared to children without MD using multinomial logistic regression models: (1) unadjusted; (2) adjusted for all sociodemographic factors; (3) adjusted for all sociodemographic and perinatal factors; and (4) adjusted for all sociodemographic, perinatal and neonatal factors; all taking into consideration clustering within multiple pairs, with country modelled as a fixed effect, and with the use of inverse probability weighting (IPW) to take into account loss to follow-up and multiple imputed dataset.

^aDefined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.

Supplemental material – Chapter 6

Table S1. Characteristics associated with lost to follow-up.

Table S2. Participants included in the analysis vs participants in the study follow-up excluded from the main analysis.

Table S3. Social and clinical characteristics associated with receiving motor-related health care among children without CP at risk of movement difficulties or with significant movement difficulties.

Table S4. Cognitive, behavioural, and socioemotional problems associated with receiving motor-related health care among extremely preterm children at risk of movement difficulties or with significant movement difficulties.

Figure S1. Participation flowchart.

Figure S2. Percentages of children born extremely preterm who received motor-related health care with 95% confidence intervals according to motor status overall and by country.

Table S1. Characteristics associated with loss to follow-up.

		Followed up N=1021 N(%)	Not followed up N=633 N(%)	Followed up vs Not followed up	
				P-value	P-value*
Maternal age at childbirth (years)	≤24	121(11.9)	151(24.0)	<0.001	<0.001
	25-34	610(60.0)	353(56.2)		
	≥35	286(28.1)	124(19.7)		
	Missing	4(0.4)	5(0.8)		
	Mean (SD)	31.1(5.8)	29.0(6.0)		
Maternal country of birth	Not foreign-born	776(80.2)	383(68.0)	<0.001	<0.001
	Born in another European country	47(4.9)	42(7.5)		
	Born in a non-European country	144(14.9)	138(24.5)		
	Missing	54(5.3)	70(11.1)		
Parity	Nulliparous	604(59.9)	335(53.7)	0.014	0.009
	Multiparous	405(40.1)	289(46.3)		
	Missing	12(1.2)	9(1.4)		
Multiple birth	Singleton	733(71.8)	469(74.1)	0.308	0.292
	Multiple	288(28.2)	164(25.9)		
	Missing	0(0.0)	0(0.0)		
PROM¹		264(26.2)	175(28.9)	0.228	0.183
	Missing	12(1.2)	28(4.4)		
Pre-eclampsia/ Eclampsia/HELLP		113(11.2)	46(7.5)	0.017	0.027
	Missing	10(1.0)	23(3.6)		
Sex	Male	532(52.1)	337(53.2)	0.654	0.820
	Female	489(47.9)	296(46.8)		
	Missing	0(0.0)	0(0.0)		
Gestational Age (completed weeks)	≤24	132(12.9)	108(17.1)	0.112	0.652
	25	191(18.7)	111(17.5)		
	26	292(28.6)	183(28.9)		
	27	406(39.8)	231(36.5)		
	Missing	0(0.0)	0(0.0)		
	Mean (SD)	26(1)	26(1)		
Birth weight (grams)	Mean (SD)	870.2(191.2)	866.0(185.7)	0.660	0.806
SGA² (EURO-Peristat)	≤10	239(23.4)	118(18.6)	0.022	0.025
	>10	782(76.6)	515(81.4)		
	Missing	0(0.0)	0(0.0)		
Congenital anomalies		85(8.3)	50(7.9)	0.758	0.244
	Missing	0(0.0)	0(0.0)		
BPD³		333(33.4)	241(39.3)	0.018	0.646
	Missing	25(2.4)	19(3.0)		
Severe Neonatal Morbidity⁴		255(25.4)	175(28.7)	0.148	0.307
	Missing	19(1.9)	24(3.8)		
Country	Belgium	70(55.1)	57(44.9)	<0.001	
	Denmark	52(59.8)	35(40.2)		
	Estonia	38(100.0)	0(0.0)		
	France	189(71.6)	75(28.4)		
	Germany	79(42.7)	106(57.3)		
	Italy	173(77.6)	50(22.4)		
	The Netherlands	75(85.2)	13(14.8)		
	Poland	52(78.8)	14(21.2)		
	Portugal	113(72.4)	43(27.6)		
	The United Kingdom	138(38.7)	219(61.3)		
	Sweden	42(66.7)	21(33.3)		

¹PROM, Premature Rupture of Membranes; ²SGA, Small for gestational age was defined as a birth weight equal or less than the 10th percentile of European references¹⁹; ³BPD, Bronchopulmonary dysplasia, defined as oxygen dependency at 36 weeks; ⁴Defined as a composite measure of cystic periventricular leukomalacia (cPVL), intraventricular hemorrhage (IVH) grades III and IV, necrotizing enterocolitis (NEC) that required surgery or peritoneal drainage or retinopathy of prematurity (ROP) ≥ stage 3

*P value adjusted for country. Missing values not included in calculation of percentages

Table S2. Participants included in the analysis *vs.* participants in the study follow-up excluded from the main analysis due to missing data on motor function or severe neurodevelopmental impairment or missing data on health care service use.

		Participants in the follow-up excluded from the main analysis			Participants vs Total Excluded	P-value
		Participants	Missing MABC-2 and no CP or NDI	Missing HC		
		N=807 N(%)	N=151 N(%)	N=63 N(%)		
Maternal Education	Low ISCED 0-2	138(17.3)	30(20.8)	12(30.0)	0.005	
	Intermediate ISCED 3-5	341(42.8)	70(48.6)	22(55.0)		
	High ISCED 6-8	317(39.8)	44(30.6)	6(15.0)		
	Missing	11(1.4)	7(4.6)	23(36.5)		
Household unemployment	At least one parent unemployed	100(12.6)	27(18.9)	-	-	
	Other situations ¹	695(87.4)	116(81.1)	-		
	Missing	12(1.5)	8(5.3)	-		
Parental cohabitation status	Single parent or other situation	138(17.2)	23(16.0)	2(13.3)	0.658	
	Married/couple/cohabiting	666(82.8)	121(84.0)	13(86.7)		
	Missing	3(0.4)	7(4.6)	48(76.2)		
Maternal age at childbirth (years)	≤24	87(10.8)	17(11.3)	17(27.0)	0.002	
	25-34	471(58.7)	103(68.2)	36(57.1)		
	≥35	245(30.5)	31(20.5)	10(15.9)		
	Missing	4 (0.5)	0(0.0)	0(0.0)		
	Mean (SD)	31.4(5.8)	30.5(5.4)	28.8(5.6)		0.001
Maternal country of birth	Not foreign-born	637(79.2)	108(71.5)	41(65.1)	0.003	
	Born in another European country	53(6.6)	11(7.3)	3(4.8)		
	Born in a non-European country	114(14.2)	32(21.2)	19(30.2)		
	Missing	3(0.4)	0(0.0)	0(0.0)		
Parity	Nulliparous	483(60.7)	92(61.3)	29(46.0)	0.306	
	Multiparous	313(39.3)	58(38.7)	34(54.0)		
	Missing	11(1.4)	1(0.7)	0(0.0)		
Multiple birth	Singleton	576(71.4)	109(72.2)	48(76.2)	0.565	
	Multiple	231(28.6)	42(27.8)	15(23.8)		
	Missing	0(0.0)	0(0.0)	0(0.0)		
PROM²		199(24.9)	45(30.2)	20(32.3)	0.085	
	Missing	9(1.1)	2(1.3)	1(1.6)		
Pre-eclampsia/Eclampsia/HELLP		90(11.3)	19(12.6)	4(6.5)	0.843	
	Missing	9(1.1)	0(0.0)	1(1.6)		
Sex	Male	412(51.1)	87(57.6)	33(52.4)	0.191	
	Female	395(48.9)	64(42.4)	30(47.6)		
	Missing	0(0.0)	0(0.0)	0(0.0)		
Gestational age (completed weeks)	≤24	82(10.2)	35(23.2)	15(23.8)	<0.001	
	25	153(19.0)	30(19.9)	8(12.7)		
	26	239(29.6)	38(25.2)	15(23.8)		
	27	333(41.3)	48(31.8)	25(39.7)		
	Missing	0(0.0)	0(0.0)	0(0.0)		
	Mean (SD)	26(1)	26(1)	26(1)		<0.001
Birth weight (grams)	Mean (SD)	876.8(188.6)	834.12(200.6)	873.4(195.4)	0.034	
SGA³ (EURO-Peristat)	≤10	198(24.5)	29(19.2)	12(19.0)	0.099	
	>10	609(75.5)	122(80.8)	51(81.0)		
	Missing	0(0.0)	0(0.0)	0(0.0)		
Congenital anomalies		67(8.3)	14(9.3)	4(6.3)	0.959	
	Missing	0(0.0)	0(0.0)	0(0.0)		
BPD⁴		253(32.2)	56(37.6)	24(38.7)	0.120	
	Missing	22(2.7)	2(1.3)	1(1.6)		
Severe Neonatal Morbidity⁵		194(24.5)	47(31.5)	14(23.0)	0.178	
	Missing	15(1.9)	2(1.3)	2(3.2)		

Table S2. Continued.

		Participants in the follow-up excluded from the main analysis			Participants vs Total Excluded	P-value
		Participants	Missing MABC-2 and no CP or NDI	Missing HC		
		N=807 N(%)	N=151 N(%)	N=63 N(%)		
Country	Belgium	47(5.8)	13(8.6)	10(15.9)	0.040	
	Denmark	42(5.2)	10(6.6)	0(0.0)		
	Estonia	33(4.1)	3(2.0)	2(3.2)		
	France	160(19.8)	22(14.6)	7(11.1)		
	Germany	59(7.3)	18(11.9)	2(3.2)		
	Italy	137(17.0)	35(23.2)	1(1.6)		
	The Netherlands	63(7.8)	3(2.0)	9(14.3)		
	Poland	41(5.1)	11(7.3)	0(0.0)		
	Portugal	94(11.6)	17(11.3)	2(3.2)		
	The United Kingdom	102(12.6)	9(6.0)	27(42.9)		
	Sweden	29(3.6)	10(6.6)	3(4.8)		
<i>Missing</i>	0(0.0)	0(0.0)	0(0.0)			

MABC-2, Movement Assessment Battery for Children – 2nd Edition; CP, Cerebral palsy; NDI, severe neurodevelopmental impairment; HC, Health care.

¹Other situations included student, parental leave, home parent and other; ²PROM, Premature Rupture of Membranes; ³SGA, Small for gestational age was defined as a birth weight equal or less than the 10th percentile of European references²⁸; ⁴BPD, Bronchopulmonary dysplasia, defined as oxygen dependency at 36 weeks' postmenstrual age; ⁵Defined as a composite measure of cystic periventricular leukomalacia (cPVL), intraventricular hemorrhage (IVH) grades III and IV, necrotizing enterocolitis (NEC) that required surgery or peritoneal drainage or retinopathy of prematurity (ROP) \geq stage 3

P value adjusted for country. Missing values not included in calculation of percentages

Table S3. Social and clinical characteristics associated with receiving motor-related health care among children without CP at risk of movement difficulties or with significant movement difficulties - Sensitivity analysis with inverse probability weighting (IPW).

	Model adjusted for country and MABC-2 score without IPW		Model adjusted for country and MABC-2 score with IPW		
	OR	95% CI	OR	95% CI	
Maternal age at childbirth (years)	<25	0.94	0.42-2.08	1.08	0.45-2.61
	25-34	1.04	0.60-1.80	1.05	0.80-1.83
	≥35	Ref.		Ref.	
Maternal Education	Low education ISCED 0-2	0.82	0.41-1.63	0.84	0.42-1.89
	Intermediate education ISCED 3-5	1.52	0.88-2.64	1.56	0.89-2.72
	High education ISCED 6-8	Ref.		Ref.	
Maternal country of birth	Not foreign-born	Ref.		Ref.	
	Born in another European country	1.09	0.46-2.56	1.08	0.45-2.58
	Born in a non-European country	0.29	0.13-0.64	0.28	0.12-0.64
Household unemployment	At least one parent unemployed	2.48	1.34-4.58	2.63	1.41-4.91
	Other situations ³	Ref.		Ref.	
Parental cohabitation status	Single parent or other situation	Ref.		Ref.	
	Married/couple/cohabiting	0.79	0.43-1.45	0.78	0.43-1.44
Parity	Nulliparous	Ref.		Ref.	
	Multiparous	0.72	0.43-1.20	0.73	0.44-1.21
Multiple gestation	Singleton	Ref.		Ref.	
	Multiple	1.00	0.58-1.73	0.98	0.56-1.71
PROM³	Yes	1.20	0.71-2.04	1.21	0.71-2.05
	No	Ref.		Ref.	
Pre-eclampsia/Eclampsia/HELLP⁴	Yes	1.17	0.59-2.36	1.14	0.57-2.30
	No	Ref.		Ref.	
Sex	Male	1.41	0.87-2.28	1.42	0.88-2.30
	Female	Ref.		Ref.	
Gestational Age (completed weeks)	≤24	1.18	0.55-2.54	1.21	0.56-2.61
	25	1.77	0.93-3.36	1.76	0.93-3.35
	26	0.72	0.40-1.30	0.72	0.40-1.31
	27	Ref.		Ref.	

Table S3. Continued.

		Model adjusted for country and MABC-2 score without IPW		Model adjusted for country and MABC-2 score with IPW	
		OR	95% CI	OR	95% CI
SGA⁵ (EURO-Peristat)	≤10	0.74	0.44-1.22	0.75	0.45-1.24
	>10	Ref.		Ref.	
Congenital anomalies	No	Ref.		Ref.	
	Yes	1.52	0.67-3.46	1.53	0.67-3.47
BPD⁶	No	Ref.		Ref.	
	Yes	1.43	0.86-2.37	1.44	0.87-2.38
Severe Neonatal Morbidity⁷	No	Ref.		Ref.	
	Yes	2.29	1.34-3.91	2.31	1.35-3.95
Use of specialized health care⁸	No	Ref.		Ref.	
	Yes	2.82	1.42-5.60	2.79	1.40-5.55
Use of general HC⁹	No	Ref.		Ref.	
	Yes	2.76	1.09-7.00	2.72	1.07-6.91

¹Defined as having at least one visit to a motor-related health specialist over the last year: (1) Physiotherapist or motor development or psychomotor therapist or kinesiologist, (2) occupational therapist or (3) early intervention; ²Other situations included student, parental leave, home parent and other; ³PROM, Premature Rupture of Membranes; ⁴HELLP, hemolysis, elevated liver enzymes, and low platelets; ⁵Small for gestational age was defined as a birth weight equal or less than the 10th percentile of European references¹⁸; ⁶BPD, Bronchopulmonary dysplasia, defined as oxygen dependency at 36 weeks' postmenstrual age; ⁷Defined as a composite measure of cystic periventricular leukomalacia (cPVL), intraventricular hemorrhage (IVH) grades III and IV, necrotizing enterocolitis (NEC) that required surgery or peritoneal drainage or retinopathy of prematurity (ROP) ≥ stage 3; ⁸Defined as having at least one visit in the last year to any of the following: (1) neurologist/ developmental paediatrician, (2) psychologist/ neuropsychologist or psychiatrist/neuropsychiatrist; (3) speech/language therapist; (4) ear specialist/ ear, nose and throat specialist/ hearing test; (5) eye specialist or ophthalmologist or optometrist or orthoptist; (6) respiratory specialist or allergologist, or (7) dietitian or nutritionist; ⁹Receiving general health care was defined as having at least one visit in the last year to any of the following: (1) paediatrician, (2) family doctor/ general practitioner, (3) hospital accident and emergency department/ hospitalization overnight, or (4) school nurse/ nurse/ health visitor.

NOTE: Statistically significant results in boldface print

Table S4. Cognitive, behavioral and socio-emotional problems associated with receiving motor-related health care among extremely preterm children at risk of movement difficulties or with significant movement difficulties – Sensitivity analysis with inverse probability weighting (IPW).

		Model adjusted for country			
		Model adjusted for country and MABC-2 score without IPW		Model adjusted for country and MABC-2 score with IPW	
		OR	95% CI	OR	95% CI
Cognitive Status²	No impairment	Ref.		Ref.	
	Mild impairment	1.15	0.66-1.98	1.17	0.67-2.02
	Moderate impairment	1.76	0.78-3.97	1.88	0.82-4.42
Internalizing Problems					
	Emotional Symptoms				
	Normal (scores 0-3)	Ref.		Ref.	
	Borderline (score 4)	0.79	0.36-1.73	0.80	0.36-1.76
	Abnormal (scores 5-10)	1.77	0.92-3.42	1.82	0.94-3.52
Peer Relationship Problems					
	Normal (scores 0-2)	Ref.		Ref.	
	Borderline (score 3)	1.45	0.68-3.09	1.47	0.69-3.15
	Abnormal (scores 4-10)	1.93	1.07-3.49	1.90	1.04-3.47
Externalizing Problems					
	Conduct problems				
	Normal (scores 0-2)	Ref.		Ref.	
	Borderline (score 3)	2.16	1.19-3.94	2.10	1.15-3.84
	Abnormal (scores 4-10)	0.85	0.45-1.60	0.87	0.46-1.64
	Hyperactivity/inattention				
	Normal (scores 0-5)	Ref.		Ref.	
	Borderline (score 6)	2.74	1.38-5.43	2.92	1.46-5.84
	Abnormal (scores 7-10)	1.88	1.08-3.26	1.98	1.13-3.48
Prosocial behavior					
	Normal (scores 6-10)	Ref.		Ref.	
	Borderline (scores 5)	1.83	0.82-4.08	1.82	0.82-4.07
	Abnormal (scores 0-4)	1.96	0.65-5.87	1.97	0.66-5.91
SDQ Total score³					
	Normal (scores 0-13)	Ref.		Ref.	
	Borderline (scores 14-16)	2.73	1.37-5.47	2.92	1.45-5.90
	Abnormal (scores 17-40)	1.31	0.71-2.41	1.40	0.75-2.59

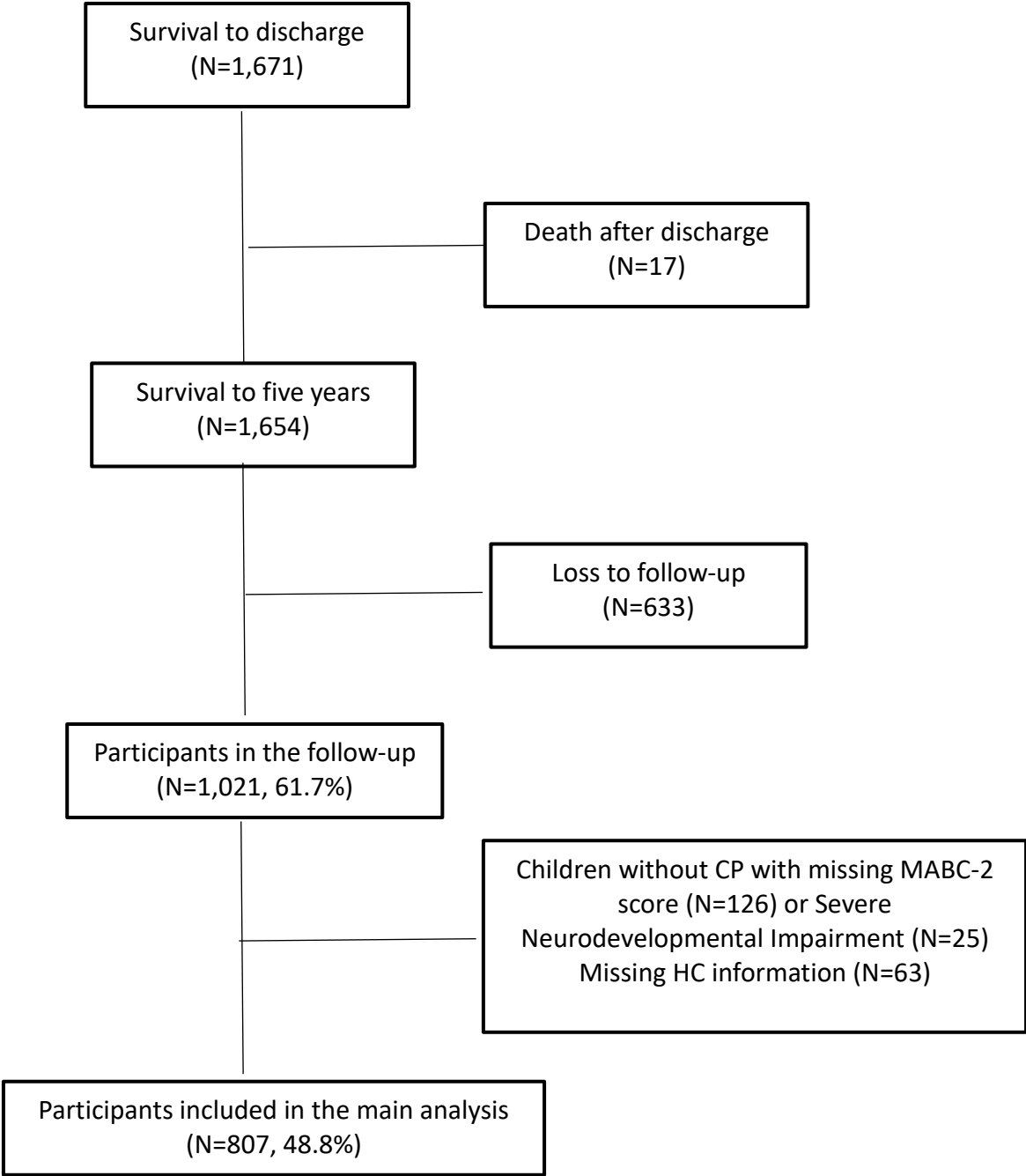
¹Motor-related health care was defined as having at least one visit to any of the following motor-related health specialists over the last year: (1) Physiotherapist or motor development or psychomotor therapist or kinesiologist, (2) occupational therapist, or (3) early intervention.

²Moderate impairment was considered if IQ between 55 to 69, mild impairment was considered if IQ between 70 to 84, no impairment was considered if IQ ≥ 85

³Strengths and Difficulties Questionnaire (SDQ) total score derived from emotional symptoms, conduct problems, hyperactivity/inattention and peer relationship problems

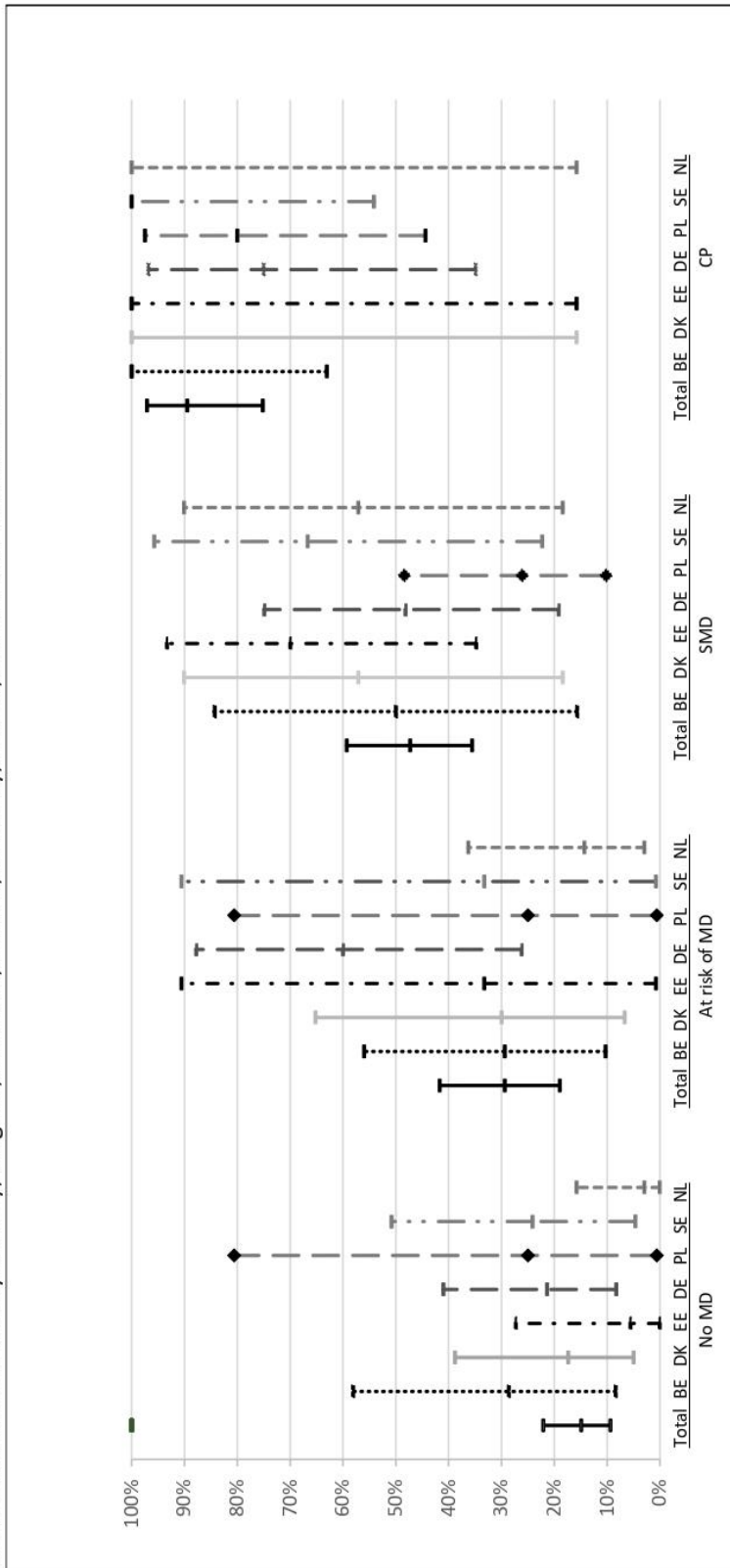
NOTE: Statistically significant results in boldface print

Figure S1. Participation flowchart.



MABC-2, Movement Assessment Battery for children-2; CP, Cerebral palsy; HC, Health Care

Figure S2. Percentage of children born extremely preterm who received motor-related health care¹ with 95% confidence intervals according to motor status overall and by country; Belgium, Denmark, Estonia, Germany, Poland, Sweden and The Netherlands.



¹Defined as having at least one visit to any motor-related health specialist over the last year: (1) Physiotherapist or motor development or psychomotor therapist or kinesiologist, (2) occupational therapist or (3) early intervention.
 MD, Movement difficulties; SMD, Significant movement difficulties; CP, Cerebral palsy; BE, Belgium; DK, Denmark; EE, Estonia; DE, Germany; PL, Poland; SE, Sweden; NL, The Netherlands; Total, combined data from the seven countries.

Supplemental material – Chapter 7

Table S1. Characteristics of children followed and lost to follow-up at 5 years of age (without IPW).

Table S2. List of the variables included in the multiple imputation by chained equations and IPW programs.

Table S3. Characteristics of children included in the study with a MABC-2 score and comparison with children without MABC-2 score and without CP (without IPW).

Table S4. Characteristics of children included in the study and comparison with children without PedsQL score (without IPW).

Table S5. Unadjusted associations of PedsQL scores with motor category for children without other moderate to severe NDI expressed in Cohen's δ effect size (standardized mean difference).

Table S6. Adjusted association of PedsQL scores with motor category – Sensitivity analyses with the use of censored regression models; in complete case without IPW, complete case with IPW, and multiple imputed dataset without IPW; and with the exclusion of children with a severe NDI in the CP group.

Figure S1. Distribution of PedsQL scores.

Figure S2. Adjusted associations of PedsQL quantiles (physical score) with motor category for children without other moderate to severe NDI.

Figure S3. Adjusted associations of PedsQL quantiles (psychosocial score) with motor category for children without other moderate to severe NDI.

Table S1. Characteristics of children followed and lost to follow-up at 5 years of age (without IPW).

	Children followed at 5 years of age		Children lost to follow-up at 5 years		<i>p-value</i> ^a
	N	%	N	%	
	1,021		633		
Sociodemographic characteristics					
Maternal age at childbirth (years)					<0.001
<25	121	11.9	151	24.0	
25-34	610	60.0	353	56.2	
≥35	286	28.1	124	19.7	
<i>Missing</i>	4	0.4	5	0.8	
Parity					0.010
First child	604	59.9	335	53.7	
Second child	252	25.0	152	24.4	
Third child or more	153	15.2	137	22.0	
<i>Missing</i>	12	1.2	9	1.4	
Maternal country of birth					<0.001
Native-born	786	77.2	384	65.3	
Other European country	67	6.6	51	8.7	
Non-European country	165	16.2	153	26.0	
<i>Missing</i>	3	0.3	45	7.1	
Perinatal and neonatal characteristics					
Gestational age (completed weeks)					0.69
≤24	132	12.9	108	17.1	
25	191	18.7	111	17.5	
26	292	28.6	183	28.9	
27	406	39.8	231	36.5	
<i>Missing</i>	0	0.0	0	0.0	
Small for gestational age					0.031
<3 rd percentile	157	15.4	73	11.5	
3-9 th percentile	82	8.0	45	7.1	
≥10 th percentile	782	76.6	515	81.4	
<i>Missing</i>	0	0.0	0	0.0	
Child sex					0.83
Female	489	47.9	296	46.8	
Male	532	52.1	337	53.2	
<i>Missing</i>	0	0.0	0	0.0	
Multiple birth					0.41
Singleton	733	71.8	469	74.1	
Multiple	288	28.2	164	25.9	
<i>Missing</i>	0	0.0	0	0.0	
Congenital anomaly					0.23
No	936	91.7	583	92.1	
Yes	85	8.3	50	7.9	
<i>Missing</i>	0	0.0	0	0.0	
Severe neonatal morbidity^b					0.31
No	747	74.6	434	71.3	
Yes	255	25.4	175	28.7	
<i>Missing</i>	19	1.9	24	3.8	
Bronchopulmonary dysplasia^c					0.54
No	642	63.9	366	59.2	
Yes	362	36.1	252	40.8	
<i>Missing</i>	17	1.7	15	2.4	
Breastfeeding at discharge					<0.001
No	447	44.7	341	56.7	
Yes	554	55.3	260	43.3	
<i>Missing</i>	20	2.0	32	5.1	

Table S1. Continued.

	Children followed at 5 years of age		Children lost to follow-up at 5 years		<i>p-value</i> ^a
	N	%	N	%	
	1,021		633		
Global					
Followed-up at 2 years of age					<i><0.001</i>
No	175	17.1	361	57.0	
Yes	846	82.9	272	43.0	
Missing	0	0.0	0	0.0	
Country (region)					
Belgium (Flanders)	70	55.1	57	44.9	
Denmark (Eastern Region)	52	59.8	35	40.2	
Estonia (entire country)	38	100.0	0	0.0	
France (Burgundy, Ile-de-France, Northern Region)	189	71.6	75	28.4	
Germany (Hesse, Saarland)	79	42.7	106	57.3	
Italy (Emilia-Romagna, Lazio, Marche)	173	77.6	50	22.4	
The Netherlands (Central Eastern)	75	85.2	13	14.8	
Poland (Wielkopolska)	52	78.8	14	21.2	
Portugal (Lisbon, Northern Region)	113	72.4	43	27.6	
The United Kingdom (East Midlands, Northern, Yorkshire and the Humber)	138	38.7	219	61.3	
Sweden (Greater Stockholm)	42	66.7	21	33.3	

Abbreviations: IPW, inverse probability weighting.

Values are frequencies (Ns rounded to a whole number) and percentages (% excluding missing values and rounded to one decimal), all without the use of inverse probability weighting (IPW).

^aP-values from Wald test of logistic regressions adjusted on country and taking into consideration clustering within multiple pairs.

^bIncluded intraventricular hemorrhage grade III/IV, cystic periventricular leukomalacia, retinopathy of prematurity stage III or more, and surgical necrotizing enterocolitis.

^cDefined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.

Table S2. List of the variables included in the multiple imputation by chained equations and IPW programs.

Perinatal/Neonatal			Sociodemographic
Previous caesarean section	Gestational age	Severe neonatal morbidity ^a	Maternal age at childbirth
Antepartum hemorrhage after week 20	Small for gestational age	Bronchopulmonary dysplasia ^b	Maternal country of birth
Admission for preterm labor/contractions after week 20	Birthweight	Any surgery before discharge	Maternal parity before childbirth
The mother has preeclampsia/eclampsia/HELLP	Apgar score <7	Use of any continuous positive airway pressure	Country
Premature rupture of membranes (>12hours)	Child sex	Use of mechanical ventilation	
Antenatal corticosteroids	Multiple pregnancy	Prophylactic surfactant in the 2 hours after birth	
Delivery in a level 3 maternity unit	Hospital transfer during neonatal care	Breastfeeding at discharge	
Mode of delivery	Congenital anomalies		

Abbreviations: IPW, inverse probability weighting. HELLP syndrome, Hemolysis, Elevated Liver enzyme, Low Platelets syndrome.

^aIncluded intraventricular hemorrhage grade III/IV, cystic periventricular leukomalacia, retinopathy of prematurity stage III or more, and surgical necrotizing enterocolitis.

^bDefined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.

Table S3. Characteristics of children included in the study with a MABC-2 score and comparison with non-CP children without MABC-2 score (without IPW).

	Non-CP children followed at 5 years with a MABC-2 score		Non-CP children followed at 5 years without MABC-2 score		<i>p-value^b</i>
	N	%	N	%	
	773		116 ^a		
Sociodemographic characteristics					
Maternal age at childbirth (years)					<0.001
<25	89	11.5	13	11.2	
25-34	451	58.5	85	73.3	
≥35	231	30.0	18	15.5	
Maternal cohabiting status					0.94
Married/couple/cohabiting	621	85.4	98	86.7	
Single/Other	106	14.6	15	13.3	
Maternal educational level					0.47
Low education ISCED 0-2	132	17.8	19	17.1	
Intermediate education ISCED 3-5	320	43.1	59	53.2	
High education ISCED 6-8	290	39.1	33	29.7	
Household unemployment status					0.11
Employed or other situation ^c	633	87.9	90	81.1	
At least one parent unemployed	87	12.1	21	18.9	
Parity at childbirth					0.28
Primiparous	464	60.7	76	66.1	
Multiparous	300	39.3	39	33.9	
Maternal country of birth					0.98
Native-born	603	78.3	91	78.4	
European born	51	6.6	7	6.0	
Non-European born	116	15.1	18	15.5	

Table S3. Continued.

	Non-CP children followed at 5 years with a MABC-2 score		Non-CP children followed at 5 years without MABC-2 score		<i>p-value</i> ^b
	N	%	N	%	
	773		116 ^a		
Perinatal and neonatal characteristics					
Gestational age (completed weeks)					<i>0.068</i>
≤24	85	11.0	18	15.5	
25	132	17.1	25	21.6	
26	233	30.1	30	25.9	
27	323	41.8	43	37.1	
Small for gestational age					<i>0.20</i>
<3rd percentile	124	16.0	15	12.9	
3-9th percentile	67	8.7	7	6.0	
≥10th percentile	582	75.3	94	81.0	
Child sex					<i>0.17</i>
Female	393	50.8	51	44.0	
Male	380	49.2	65	56.0	
Multiple birth					<i>0.94</i>
Singleton	551	71.3	84	72.4	
Multiple	222	28.7	32	27.6	
Congenital anomaly					<i>0.76</i>
No	715	92.5	105	90.5	
Yes	58	7.5	11	9.5	
Severe neonatal morbidity^d					<i>0.073</i>
No	608	80.2	84	73.7	
Yes	150	19.8	30	26.3	
Bronchopulmonary dysplasia^e					<i>0.30</i>
No	505	66.4	76	66.7	
Yes	256	33.6	38	33.3	
Breastfeeding at discharge					<i>0.001</i>
No	312	41.0	67	59.8	
Yes	449	59.0	45	40.2	

Abbreviations: MABC-2, Movement Assessment Battery for Children – 2nd Edition. CP, cerebral palsy. IPW, inverse probability weighting. ISCED, International Standard Classification of Education. [ref ISCED, 2011]

Values are frequencies (Ns rounded to a whole number) and percentages (% excluding missing values and rounded to one decimal), all without the use of inverse probability weighting (IPW).

^aAmong the 116 non-CP children followed at 5 years without MABC-2 score, 87 were followed by parental questionnaire and 29 had a clinical assessment but an incomplete or missing MABC-2.

^bP-values from Wald test of logistic regressions adjusted on country and taking into consideration clustering within multiple pairs.

^cOther situation included student, parental leave, home parent and other.

^dIncluded intraventricular haemorrhage grade III/IV, cystic periventricular leukomalacia, retinopathy of prematurity stage III or more, and surgical necrotizing enterocolitis.

^eDefined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.

Table S4. Characteristics of children included in the study and comparison with children without PedsQL score (without IPW).

	Children included in the study		Children without PedsQL score		<i>p-value</i> ^b
	N	%	N	%	
	810		63 ^a		
Sociodemographic characteristics					
Maternal age at childbirth (years)					<i>0.034</i>
<25	88	10.9	16	25.4	
25-34	473	58.7	37	58.7	
≥35	245	30.4	10	15.9	
Maternal cohabiting status					<i>/^c</i>
Married/couple/cohabiting	691	85.4	n.a.	n.a.	
Single/Other	118	14.6	n.a.	n.a.	
Maternal educational level					<i>/^c</i>
Low education ISCED 0-2	137	17.1	n.a.	n.a.	
Intermediate education ISCED 3-5	346	43.3	n.a.	n.a.	
High education ISCED 6-8	316	39.5	n.a.	n.a.	
Household unemployment status					<i>/^c</i>
Employed or other situation ^d	699	87.4	n.a.	n.a.	
At least one parent unemployed	101	12.6	n.a.	n.a.	
Parity at childbirth					<i>0.003</i>
Primiparous	487	61.0	25	39.7	
Multiparous	312	39.0	38	60.3	
Maternal country of birth					<i>0.003</i>
Native-born	639	79.2	41	65.1	
European born	51	6.3	5	7.9	
Non-European born	117	14.5	17	27.0	

Table S4. Continued.

	Children included in the study		Children without PedsQL score		<i>p-value</i> ^b
	N	%	N	%	
	810		63 ^a		
Perinatal and neonatal characteristics					
Gestational age (completed weeks)					<i>0.064</i>
≤24	85	10.5	13	20.6	
25	152	18.8	9	14.3	
26	239	29.5	17	27.0	
27	334	41.2	24	38.1	
Small for gestational age					<i>0.25</i>
<3rd percentile	123	15.2	13	20.6	
3-9th percentile	70	8.6	4	6.3	
≥10th percentile	617	76.2	46	73.0	
Child sex					<i>0.11</i>
Female	401	49.5	24	38.1	
Male	409	50.5	39	61.9	
Multiple birth					<i>0.50</i>
Singleton	576	71.1	48	76.2	
Multiple	234	28.9	15	23.8	
Congenital anomaly					<i>0.82</i>
No	744	91.9	58	92.1	
Yes	66	8.1	5	7.9	
Severe neonatal morbidity^e					<i>0.74</i>
No	600	75.6	47	75.8	
Yes	194	24.4	15	24.2	
Bronchopulmonary dysplasia^f					<i>0.44</i>
No	522	65.6	31	50.0	
Yes	274	34.4	31	50.0	
Breastfeeding at discharge					<i>0.027</i>
No	330	41.6	34	54.0	
Yes	464	58.4	29	46.0	

Abbreviations: PedsQL, Pediatric Quality of Life Inventory™. IPW, inverse probability weighting. n.a., not available. ISCED, International Standard Classification of Education. [ref ISCED, 2011]

Values are frequencies (Ns rounded to a whole number) and percentages (% excluding missing values and rounded to one decimal), all without the use of inverse probability weighting (IPW) to correct for loss to follow-up.

^aIncluded the exclusion of 16 children in the category no movement difficulties (MD), 11 in the category at risk of MD, 21 in the category significant MD, and 15 in the category cerebral palsy (CP).

^bP-values from Wald test of logistic regressions adjusted on country and taking into consideration clustering within multiple pairs.

^c49 out of the 63 children (77.8%) without PedsQL score have been followed by clinical assessment only and information on this characteristic was part of the parental questionnaire; comparing the two columns appeared irrelevant.

^dOther situation included student, parental leave, home parent and other.

^eIncluded intraventricular haemorrhage grade III/IV, cystic periventricular leukomalacia, retinopathy of prematurity stage III or more, and surgical necrotizing enterocolitis.

^fDefined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.

Table S5. Unadjusted associations of PedsQL scores with motor category for children without other moderate to severe NDI expressed in Cohen’s δ effect size (standardized mean difference).

	PedsQL Physical Health Summary Score Cohen’s δ [95% CI] ^a	PedsQL Psychosocial Health Summary Score Cohen’s δ [95% CI]	PedsQL Total Scale Score Cohen’s δ [95% CI]
Main analysis			
No MD	REF	REF	REF
At risk of MD	0.31 [0.13, 0.50]	0.37 [0.18, 0.55]	0.39 [0.20, 0.57]
Significant MD	0.62 [0.45, 0.80]	0.50 [0.32, 0.67]	0.63 [0.45, 0.81]
CP	1.94 [1.67, 2.21]	1.54 [1.28, 1.80]	1.98 [1.70, 2.25]
Sub-group analysis – After exclusion of children with other moderate to severe NDI (N=687)^b			
No MD	REF	REF	REF
At risk of MD	0.31 [0.12, 0.50]	0.40 [0.21, 0.59]	0.41 [0.22, 0.60]
Significant MD	0.60 [0.40, 0.80]	0.38 [0.19, 0.58]	0.55 [0.35, 0.74]
CP	1.61 [1.27, 1.96]	1.16 [0.82, 1.50]	1.53 [1.18, 1.88]

Abbreviations: PedsQL, Pediatric Quality of Life Inventory™. Cohen’s δ , Cohen’s δ effect size (standardized mean difference). CI, confidence interval. MD, movement difficulties. REF, reference category. CP, cerebral palsy. NDI, neurodevelopmental impairment.

^aPedsQL score reductions expressed in Cohen’s δ effect size (standardized mean difference) rounded to two decimals. All analyses in complete case analysis and without the use of inverse probability weighting (IPW) as it is not supported with the command “esize” in Stata.

^bChildren with moderate to severe cognitive (full scale intelligence quotient (IQ) <70 (<-2SD)), hearing or visual impairment (implant or hearing aid or deafness; blindness or difficulty seeing even with glasses).

Table S6. Adjusted association of PedsQL scores with motor category – Sensitivity analyses with the use of censored regression models; in complete case without IPW, complete case with IPW, and multiple imputed dataset without IPW; and with the exclusion of children with a severe NDI in the CP group.

	PedsQL Physical Health Summary Score β [95% CI] ^a	PedsQL Psychosocial Health Summary Score β [95% CI]	PedsQL Total Scale Score β [95% CI]
Main analysis – Linear regression			
No MD	REF	REF	REF
At risk of MD	-5.4 [-9.1, -1.6]	-4.9 [-7.6, -2.1]	-5.0 [-7.7, -2.3]
Significant MD	-11.9 [-16.1, -7.8]	-7.4 [-10.3, -4.5]	-9.1 [-12.0, -6.1]
CP	-35.3 [-42.7, -27.9]	-20.6 [-25.2, -16.0]	-26.1 [-31.0, -21.2]
Sensitivity analysis – Tobit censored regression^b			
No MD	REF	REF	REF
At risk of MD	-6.9 [-10.9, -2.8]	-5.4 [-8.0, -2.8]	-5.5 [-8.0, -3.0]
Significant MD	-11.9 [-16.5, -7.3]	-6.7 [-9.4, -4.0]	-8.1 [-10.8, -5.4]
CP	-36.4 [-42.9, -30.0]	-20.2 [-24.1, -16.2]	-25.3 [-29.4, -21.2]
Sensitivity analysis – CLAD censored regression^{b,c}			
No MD	REF	REF	REF
At risk of MD	-2.7 [-5.6, 2.4]	-4.4 [-7.9, -1.3]	-4.5 [-7.8, -1.8]
Significant MD	-9.6 [-16.6, -4.5]	-6.5 [-10.2, -2.6]	-9.2 [-13.6, -6.2]
CP	-38.3 [-49.5, -26.3]	-23.5 [-30.1, -18.0]	-29.6 [-35.9, -24.0]
Sensitivity analysis – Complete case without IPW			
No MD	REF	REF	REF
At risk of MD	-5.9 [-9.3, -2.5]	-5.2 [-7.7, -2.6]	-5.4 [-8.0, -2.9]
Significant MD	-10.7 [-14.7, -6.7]	-6.4 [-9.1, -3.8]	-8.0 [-10.8, -5.3]
CP	-34.0 [-40.2, -27.8]	-19.9 [-23.9, -15.9]	-25.1 [-29.3, -21.0]
Sensitivity analysis – Complete case with IPW			
No MD	REF	REF	REF
At risk of MD	-5.3 [-9.1, -1.6]	-5.1 [-7.9, -2.4]	-5.2 [-7.9, -2.5]
Significant MD	-11.0 [-15.3, -6.7]	-6.5 [-9.5, -3.5]	-8.2 [-11.3, -5.2]
CP	-37.2 [-44.3, -30.1]	-20.9 [-25.8, -16.0]	-27.0 [-31.9, -22.1]
Sensitivity analysis – Multiple imputed dataset without IPW			
No MD	REF	REF	REF
At risk of MD	-5.5 [-8.9, -2.1]	-4.8 [-7.4, -2.3]	-5.1 [-7.6, -2.6]
Significant MD	-11.0 [-14.9, -7.1]	-6.8 [-9.5, -4.2]	-8.4 [-11.1, -5.7]
CP	-33.6 [-39.7, -27.5]	-19.9 [-23.7, -16.0]	-24.9 [-29.0, -20.9]

Table S6. Continued.

	PedsQL Physical Health Summary Score β [95% CI]^a	PedsQL Psychosocial Health Summary Score β [95% CI]	PedsQL Total Scale Score β [95% CI]
Sensitivity analysis – With exclusion of children with a severe NDI in the CP group (n=15)^d			
No MD	REF	REF	REF
At risk of MD	-5.6 [-9.3, -1.9]	-5.0 [-7.7, -2.4]	-5.2 [-7.9, -2.5]
Significant MD	-12.2 [-16.4, -8.1]	-7.5 [-10.4, -4.6]	-9.3 [-12.2, -6.3]
CP	-28.0 [-34.9, -21.0]	-18.6 [-22.7, -14.5]	-22.0 [-26.5, -17.6]

Abbreviations: PedsQL, Pediatric Quality of Life Inventory™. IPW, inverse probability weighting. NDI, neurodevelopmental impairment. CP, cerebral palsy. β, Beta. CI, confidence interval. MD, movement difficulties. REF, reference category. CLAD, censored least absolute deviations (model). MICE, multiple imputation by chained equations. IQ, intelligence quotient. SD, standard deviation.

^aPedsQL score reductions expressed in Beta and their 95% confidence intervals (β [95% CI]) rounded to one decimal.

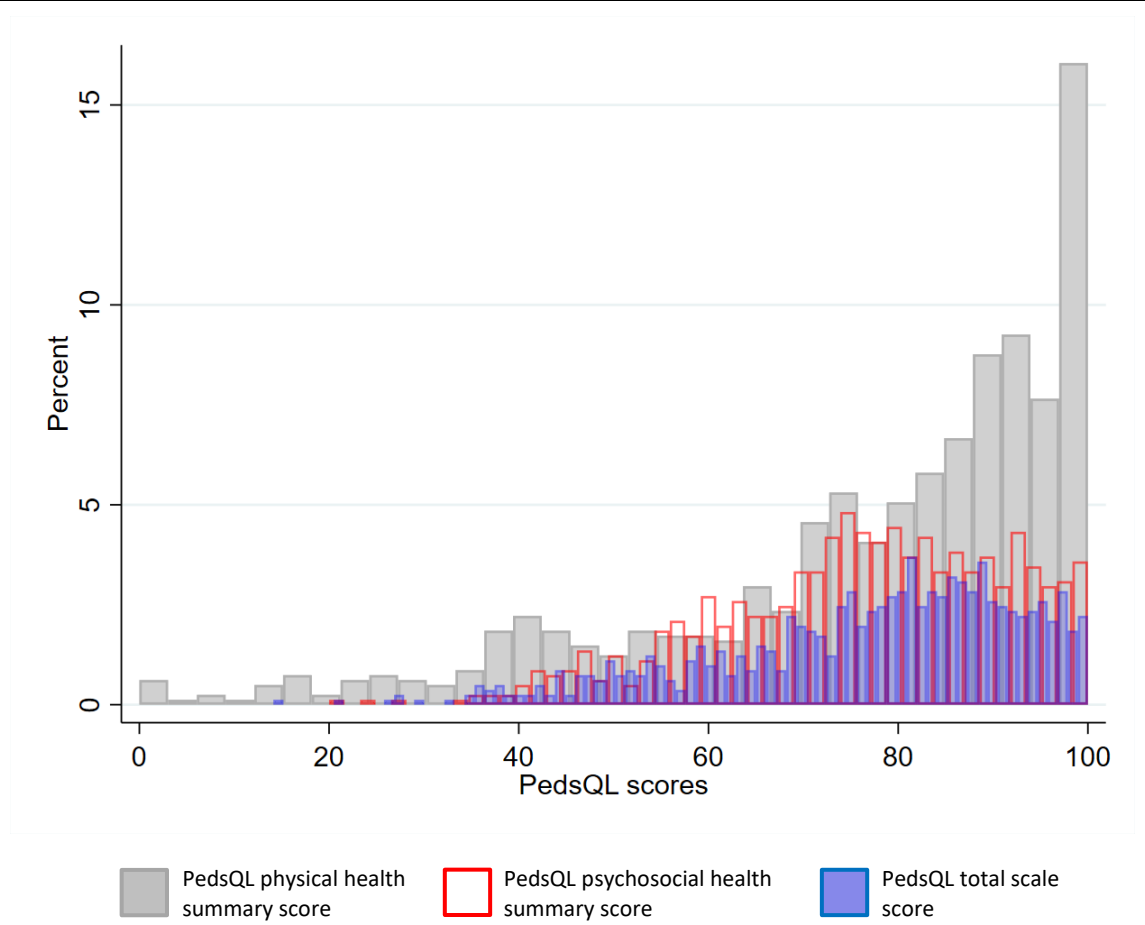
All analyses were adjusted on child age and sex, and family sociodemographic characteristics including maternal age and parity at childbirth, maternal country of birth, parental cohabiting status, maternal educational level and household unemployment status.

^bFor this sensitivity analysis using the censored regression models, namely the Tobit and the censored least absolute deviations (CLAD) models, the results in complete case analysis and without the use of inverse probability weighting (IPW) are the basis of comparison as the CLAD model is not supported after multiple imputation by chained equations (MICE) and/or IPW in Stata.

^cCLAD estimates of confidence intervals using bias-corrected methods with 1,000 bootstrap replications.

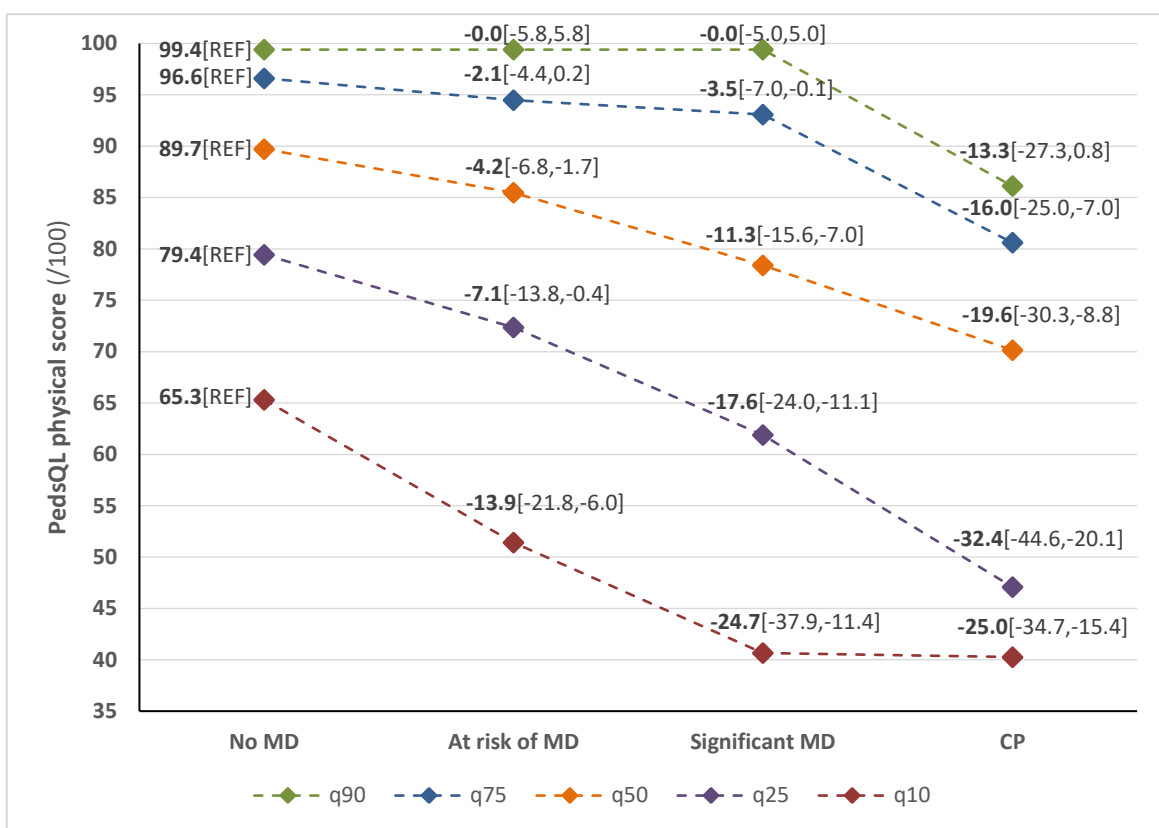
^dNeurodevelopmental impairment (NDI) integrated cognitive, hearing and visual impairment. Severe NDI defined as an intelligence quotient (IQ) <55 (<-3SD), deafness or difficulties hearing even with hearing aids or implants or blindness or seeing light only.

Figure S1. Distribution of PedsQL scores.



Abbreviations: PedsQL, Pediatric Quality of Life Inventory™.

Figure S2. Adjusted associations of PedsQL quantiles (physical score) with motor category for children without other moderate to severe NDI.

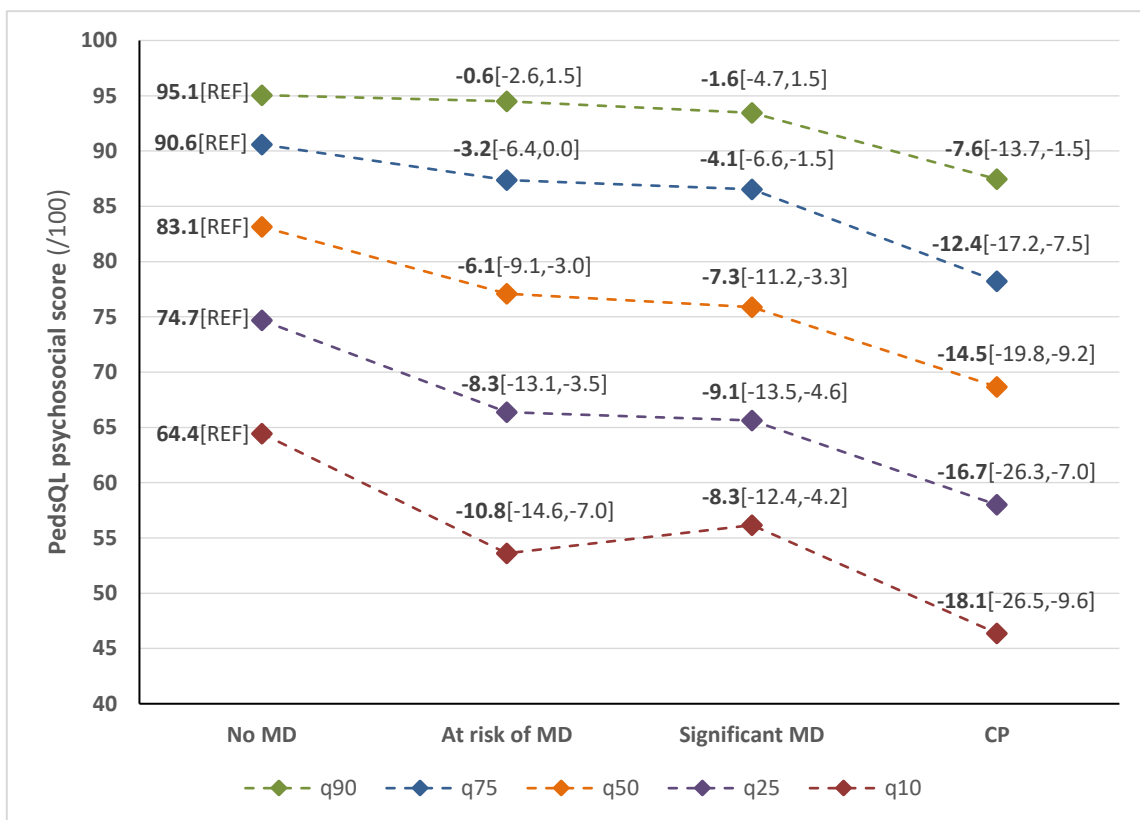


Abbreviations: PedsQL, Pediatric Quality of Life Inventory™. REF, reference category. MD, movement difficulties. CP, cerebral palsy. q90, quantile 90; q75, quantile 75; q50, quantile 50; q25, quantile 25; q10, quantile 10.

PedsQL physical score [REF] and reductions expressed in Beta and their 95% confidence intervals (β [95% CI]) rounded to one decimal, all with the use of inverse probability weighting (IPW) to correct for loss to follow-up; adjustment on child age and sex, and family sociodemographic characteristics including maternal age and parity at childbirth, maternal country of birth, parental cohabiting status, maternal educational level and household unemployment status; and exclusion of children with a moderate to severe neurodevelopmental impairment (NDI) (cognitive (full scale intelligence quotient (IQ) <70 (<-2SD)), hearing or visual impairment (implant or hearing aid or deafness; blindness or difficulty seeing even with glasses)).

As illustrative example, for the quantile 50 (q50), the reference value (category no MD) is 89.7 and we observed reductions of the PedsQL physical score expressed in Beta and their 95% confidence intervals (β [95% CI]) of -4.2 [-6.8, -1.7], -11.3 [-15.6, -7.0] and -19.6 [-30.3, -8.8] for the categories at risk of MD, significant MD and CP, respectively, in comparison to the reference category.

Figure S3. Adjusted associations of PedsQL quantiles (psychosocial score) with motor category for children without other moderate to severe NDI.



Abbreviations: PedsQL, Pediatric Quality of Life Inventory™. REF, reference category. MD, movement difficulties. CP, cerebral palsy. q90, quantile 90; q75, quantile 75; q50, quantile 50; q25, quantile 25; q10, quantile 10.

PedsQL psychosocial score [REF] and reductions expressed in Beta and their 95% confidence intervals (β [95% CI]) rounded to one decimal, all with the use of inverse probability weighting (IPW) to correct for loss to follow-up; adjustment on child age and sex, and family sociodemographic characteristics including maternal age and parity at childbirth, maternal country of birth, parental cohabiting status, maternal educational level and household unemployment status; and exclusion of children with a moderate to severe neurodevelopmental impairment (NDI) (cognitive (full scale intelligence quotient (IQ) <70 (<-2SD)), hearing or visual impairment (implant or hearing aid or deafness; blindness or difficulty seeing even with glasses)).

As illustrative example, for the quantile 50 (q50), the reference value (category no MD) is 83.1 and we observed reductions of the PedsQL total score expressed in Beta and their 95% confidence intervals (β [95% CI]) of -6.1 [-9.1, -3.0], -7.3 [-11.2, -3.3] and -14.5 [-19.8, -9.2] for the categories at risk of MD, significant MD and CP, respectively, in comparison to the reference category.

Long abstract in French (Résumé substantiel en français)

Titre : Difficultés motrices des enfants nés très grands prématurés : facteurs de risque et conséquences sur la qualité de vie.

Les enfants nés très grand prématurés (TGP, avant 28 semaines d'âge gestationnel), ont vu leur chance de survie augmenter ces dernières décennies grâce à d'importantes avancées dans la prise en charge obstétricale et néonatale. Cependant, ces enfants continuent d'être plus à risque de problèmes du développement que leurs homologues nés à terme. Les problèmes de développement moteur, comprenant la paralysie cérébrale (PC), le trouble développemental de la coordination (TDC) et d'autres troubles moteurs (TM) sont fréquents dans cette population. La PC est une conséquence bien documentée de la naissance TGP avec une prévalence autour de 10 % dans les études contemporaines, une fréquence 100 fois plus importante que chez les enfants nés à terme. La prévalence des TM est, quant à elle, moins bien établie avec des variations considérables d'une étude à l'autre : allant de 8 % à plus de 40 %. Ces problèmes moteurs réduisent les possibilités de développement de l'enfant dans de multiples domaines et ont été associés à une altération du développement cognitif, des performances scolaires, de l'intégration sociale et du fonctionnement à l'âge adulte.

Malgré les conséquences de la très grande prématurité à court et à long terme, notre compréhension de la situation reste limitée, et ce particulièrement chez les enfants sans PC pour lesquels nous disposons de moins d'études. Une meilleure compréhension de l'éventail des déficiences motrices dont souffrent les enfants nés TGP et des caractéristiques cliniques et sociales associées est essentielle dans la mise en œuvre d'interventions précoces ou dans la recherche d'un suivi optimal de la part des professionnels de santé. Afin de mieux détecter et soutenir les enfants présentant des problèmes de développement moteur, il est maintenant recommandé d'évaluer le développement moteur des enfants nés TGP au cours des premières années de vie. En effet, des études ont montré les bénéfices des interventions visant à améliorer les performances motrices enfants nés TGP. Cependant, les informations sur l'utilisation des services de santé par les enfants nés TGP et présentant des problèmes moteurs sont rares. Enfin, malgré le fait que l'altération des fonctions motrices puisse impacter les activités quotidiennes, la scolarité et les relations sociales, les conséquences des problèmes moteurs sur la vie et le bien-être des enfants TGP sont peu décrites.

Au regard des connaissances énoncées précédemment, ce travail de doctorat visait donc à i) estimer la prévalence de la PC et du TM en l'absence de PC chez les enfants nés TGP ; ii)

explorer les facteurs de risque sociodémographiques, périnataux et néonataux associés à ces problèmes moteurs ; iii) étudier l'utilisation des services de santé par les enfants nés TGP et présentant des problèmes moteurs ; et iv) mesurer l'impact des problèmes moteurs sur la qualité de vie liée à la santé (QdVLS) de l'enfant.

Nos travaux ont utilisé les données d'une cohorte de naissance TGP en population en 2011-2012 dans 19 régions d'11 pays d'Europe. Les données périnatales et néonatales ont été recueillies à partir des dossiers obstétricaux et néonataux pendant l'hospitalisation néonatale par le personnel médical ou des enquêteurs formés. À deux ans (âge corrigé) et à cinq ans (âge chronologique), les parents ont rempli des questionnaires sur le développement, la santé et l'utilisation des services de santé par leur enfant, ainsi que sur le contexte familial et social. Dans le cadre du suivi à cinq ans, les enfants nés TGP ont également été invités à effectuer une évaluation clinique portant sur le fonctionnement neurocognitif et moteur. À cinq ans, les parents rapportaient également un éventuel diagnostic clinique de PC et remplissaient un questionnaire sur la QdVLS de leur enfant (*PedsQL, Pediatric Quality of Life InventoryTM*). Les performances motrices des enfants ont été évaluées à l'aide du *Movement Assessment Battery for Children – 2nd Edition* (MABC-2) et les enfants sans PC ont été classés en fonction d'un score percentile ajusté sur l'âge comme n'ayant pas de TM (>15^e percentile), étant à risque de TM (6^e-15^e percentile) ou ayant des TM manifestes (≤5^e percentile).

Au cours de ce travail de doctorat, nous avons pu générer de nouvelles connaissances sur les problèmes de développement moteur rencontrés par les enfants nés TGP. Tout d'abord, nous avons constaté que plus de 50 % des enfants nés TGP présentaient des TM en l'absence de PC à l'âge de cinq ans, avec 23,2 % catégorisés à risque de TM et 31,7 % avec des TM manifestes. Contrairement à la prévalence de la PC, pour laquelle la plupart des études contemporaines rapportaient des estimations autour de 10 %, un résultat que nous avons également trouvé dans nos travaux (prévalence pondérée de 11,1 %) ; d'importantes variations dans l'estimation des prévalences de TM étaient observées entre les études publiées. Au total, ce sont donc environ 60% des enfants nés TGP qui sont confrontés à des problèmes de développement moteur, soulignant l'enjeu de santé publique que cela représente.

En parallèle, nous avons exploré les facteurs de risque sociodémographiques, périnataux et néonataux des TM sans PC. En effet, les recherches existantes dans la littérature sur les facteurs de risque des TM sans PC ne permettent pas de conclure en dehors d'une association avec la naissance prématurée et le sexe masculin de l'enfant. Concernant les

facteurs de risque périnataux et néonataux associés au risque de TM et la présence de TM manifestes, nous avons constaté que certains facteurs étaient fortement associés aux deux catégories de TM, à savoir, être petit pour l'âge gestationnel, le sexe masculin et la dysplasie bronchopulmonaire, tandis que d'autres facteurs étaient associés aux TM manifestes uniquement : l'âge gestationnel, les anomalies congénitales, les lésions cérébrales sévères (combinant les hémorragies intraventriculaires de grade III ou IV et les leucomalacies périventriculaires – lésions de la substance blanche périventriculaire) et les corticostéroïdes postnataux. Tous ces résultats fournissent des informations pour optimiser l'identification des enfants à risque qui pourraient bénéficier d'interventions précoces visant à améliorer leur statut moteur sur le long terme. Nous avons également trouvé plusieurs facteurs sociodémographiques associés aux TM. Le fait d'avoir au moins un parent au chômage était associé à la fois au risque de TM et aux TM manifestes, tandis que le jeune âge de la mère, son bas niveau d'étude et sa naissance dans un pays extérieur à l'Europe étaient associés au fait d'avoir des TM manifestes. Dans la littérature, certaines études avaient déjà rapporté des associations avec des facteurs sociodémographiques, mais la plupart du temps, très peu de facteurs étaient analysés et principalement chez des jeunes enfants âgés de moins de cinq ans. Ces résultats illustrent l'importance de prendre en compte le contexte social dans les programmes de santé publique destinés aux enfants nés TGP. Par ailleurs, comprendre comment les facteurs sociaux peuvent interagir avec les risques médicaux et biologiques est une piste de recherche importante afin de mieux cibler les groupes à risque et comprendre les mécanismes de risque et de résilience.

D'autre part, certains chercheurs ont avancé l'idée d'un continuum possible entre la PC et les TM, avec les TM manifestes en présence de dysfonctionnements neurologiques pouvant être considérés comme des troubles très proches des PC. Les changements dans les politiques de soins et l'amélioration de la prise en charge de la PC ont permis de réduire l'incidence des PC lors des dernières décennies. Or, sur la même période, l'incidence des TM est restée stable voire a augmenté dans certaines études, et cette divergence d'évolution n'est pas encore bien expliquée. Aussi, il est légitime de se demander si les enfants qui auraient pu développer une PC auparavant sont aujourd'hui dans le groupe d'enfants ayant des TM manifestes. Cependant, la plupart des études évaluant la performance motrice des enfants nés TGP considèrent la PC comme un trouble spécifique et excluent ces enfants des analyses, et *vice versa*. À ce jour, une seule revue systématique a regardé les facteurs de risque de PC et de TM en l'absence de PC dans le même article.

Nous avons donc, dans un deuxième temps, comparé les facteurs de risque sociodémographiques, périnataux et néonataux de ces deux problèmes de développement moteur. Le jeune âge de la mère, le sexe masculin et la dysplasie bronchopulmonaire étaient associés à la fois à un risque augmenté de PC et de TM. En revanche, les associations étaient différentes pour les autres facteurs. Aussi, les facteurs de risque fortement associés à la PC étaient les lésions cérébrales (tous les grades d'hémorragies intraventriculaires et les leucomalacies périventriculaires), les autres comorbidités néonatales, les anomalies congénitales et un faible score Apgar à 5 minutes. De son côté, les facteurs de risque associés aux TM étaient la primiparité, le bas niveau d'étude de la mère, et le fait d'être petit pour l'âge gestationnel. Les hémorragies cérébrales sévères (grades III et IV) et les leucomalacies périventriculaires étaient associées aux TM mais à un plus faible ordre de grandeur que pour la PC. L'âge gestationnel était associé à la fois à la PC et aux TM, mais cette association s'estompait pour la PC après ajustement sur les comorbidités néonatales. À l'exception du jeune âge de la mère, les autres facteurs sociodémographiques semblent plus influencer le risque de TM que celui de PC. Pour conclure sur ce point, même si nous avons observé des similitudes avec certains facteurs de risque associés à la fois à la PC et aux TM, les profils de facteurs de risque restaient différents et donc révélateurs d'étiologies probablement distinctes. Le risque de PC semble être associé à des facteurs directement en lien avec l'amélioration de la prise en charge des nouveau-nés TGP, tels que les hémorragies intraventriculaires, l'aide en oxygène, le score Apgar ou l'accouchement dans une unité de niveau 3. En revanche, les TM sont plus associés à des facteurs de risque pour lesquels nous ne savons pas encore intervenir de façon efficace, c.à.d. l'âge gestationnel, le fait d'être petit pour l'âge gestationnel ou les facteurs sociodémographiques. Cependant, afin d'améliorer la compréhension du potentiel glissement entre PC et TM, les recherches en cours qui explorent les anomalies cérébrales chez les enfants atteints de TM doivent se poursuivre.

En examinant les soutiens en matière de services de santé reçus par ces enfants, nous avons constaté que la majorité des enfants TGP ayant des TM ne consultaient pas de services de santé en lien à la motricité à l'âge de cinq ans ; c.à.d. seulement 42,8 % des enfants présentant des TM manifestes et 25,9 % des enfants à risque de TM étaient suivis. En outre, les taux de suivi variaient fortement d'un pays à l'autre. À l'inverse, et de manière rassurante, près de 90 % des enfants avec un diagnostic de PC étaient suivis par des professionnels de la santé en lien avec la motricité ; et avec des taux de suivi constants entre les pays. Par ailleurs, les enfants présentant d'autres difficultés de développement étaient plus susceptibles de

recevoir des services de santé en lien à la motricité. Ces résultats sont en faveur de l'établissement de directives internationales pour l'accompagnement des enfants nés TGP durant leurs premières années de vie. En effet, contrairement aux recommandations pour les enfants avec des PC, ces directives n'existaient pas avant 2018 pour les enfants nés TGP sans diagnostic formel de déficience, tel que les TM. Nos résultats appellent également de la formation des professionnels de santé pour mieux détecter les problèmes de développement moteurs éventuels.

Les problèmes de développement moteur étaient associés à une QdVLS moindre, avec le niveau de QdVLS le plus bas pour les enfants atteints de PC, suivis par ceux présentant des TM manifestes, et ceux à risque de TM, le tout par rapport aux enfants nés TGP sans TM. Pour l'ensemble des enfants ayant une PC, une réduction significative de la QdVLS était observée. Ce qui n'était pas le cas pour les enfants présentant des TM pour lesquels une partie d'entre eux avait une QdVLS identique à celle des enfants sans TM. Ce dernier point suggère qu'il pourrait y avoir des facteurs atténuants ou protecteurs qui préservent la QdVLS de certains enfants, et appelle donc à de futures recherches axées sur l'identification des potentiels facteurs protecteurs individuels, familiaux ou environnementaux. Les réductions de la QdVLS persistaient après l'exclusion des enfants présentant d'autres comorbidités développementales, mais également pour les enfants ne consultant pas de services de santé en lien à la motricité.

Pour conclure, la majorité des enfants nés TGP font face à des problèmes de développement moteur pendant l'enfance. En dehors de ceux atteints de PC, la plupart ne sont pas suivis par des professionnels de santé qui pourraient les aider à améliorer leurs performances motrices. Ces difficultés motrices, qu'elles soient diagnostiquées en tant que PC, ou se manifestent sous la forme d'autres TM, impactent la vie des enfants dans leurs activités quotidiennes. Et ce même pour les enfants avec des TM mineurs ou n'ayant pas d'autres comorbidités développementales. Ces résultats appellent donc à un suivi continu des enfants nés TGP pendant plusieurs années, à un meilleur diagnostic de ces difficultés et à une meilleure offre de services de santé pour les enfants présentant des problèmes moteurs afin de les accompagner au mieux dans leur développement et limiter l'impact sur leur quotidien.