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Category of study.

Population study

Impact Statement.

- 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.

Abstract

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 five-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 to 3.3), while non-CP MD was associated with primiparity, maternal education, small for GA (RRR: 1.6 to 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.

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 sequelae 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 social function and quality of life.[20]

Understanding the sociodemographic, perinatal and neonatal factors that are associated with CP and non-CP MD among EPT children is necessary to advise health care 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 gestational age 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 two and five 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 five 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 five-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 five years of age, reported by parents in the five-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 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 ≤5th percentile and no MD as >15th 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 (RC, UA, SJ, and JZ). 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 five minutes, sex, multiple birth, delivery in a level 3 maternity unit, antepartum hemorrhage after week 20, premature rupture of membranes (PROM) >12 hours, 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 hours of life).

Some factors, associated with motor impairment in the literature,[11,14,28,44] could not be included because 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., caesarean 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 modelled 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 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, 1,654 EPT-born infants were alive at five years of age and 1,021 (61.7%) were followed up (**Figure 1**). Children lost to follow-up were more likely to have social risk factors and be SGA (**Supplemental 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 socioeconomic 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 socioeconomic 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 five 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 (**Supplemental Table 3**) yielded similar conclusions. After excluding children with severe NDI (n=20) in the CP group (**Supplemental 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.

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] Further, 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 seven of nine 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 grams) 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 five 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 eight out of 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 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).

In the literature on non-CP motor impairment,[11] lower parental occupation and lower maternal education were associated with motor impairment before five 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 a good to excellent inter-rater reliability and test-retest reliability.[32] Further, the assessors were not blinded to the child's EPT status as there was no control group and some assessments were organised within local routine follow-up programs. While this could lead to some bias, there are detailed instructions for administration and objective criteria for 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 five 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 five-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 sociodemographic factors, mainly with non-CP MD, illustrate the importance of considering the social context of intervention programs for children born EPT.

Data availability statement:

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

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Main figure legend:

Figure 1. Flowchart of the study population selection from the 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. MD, movement difficulties. No MD (MABC-2 >15th percentile); at risk of MD (6th to 15th percentile); non-CP MD (≤5th percentile).

[a]Neurodevelopmental impairment (NDI) integrated cognitive, hearing and visual impairment. Severe NDI defined as an intelligence quotient (IQ) ≤54 (<-3SD), deafness or difficulties hearing even with hearing aids or implants or blindness or seeing light only.

[b]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]

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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Author Contributions:

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 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 interpretation of data, drafting the article, revising it critically for important intellectual content, and approved the final version to be published.

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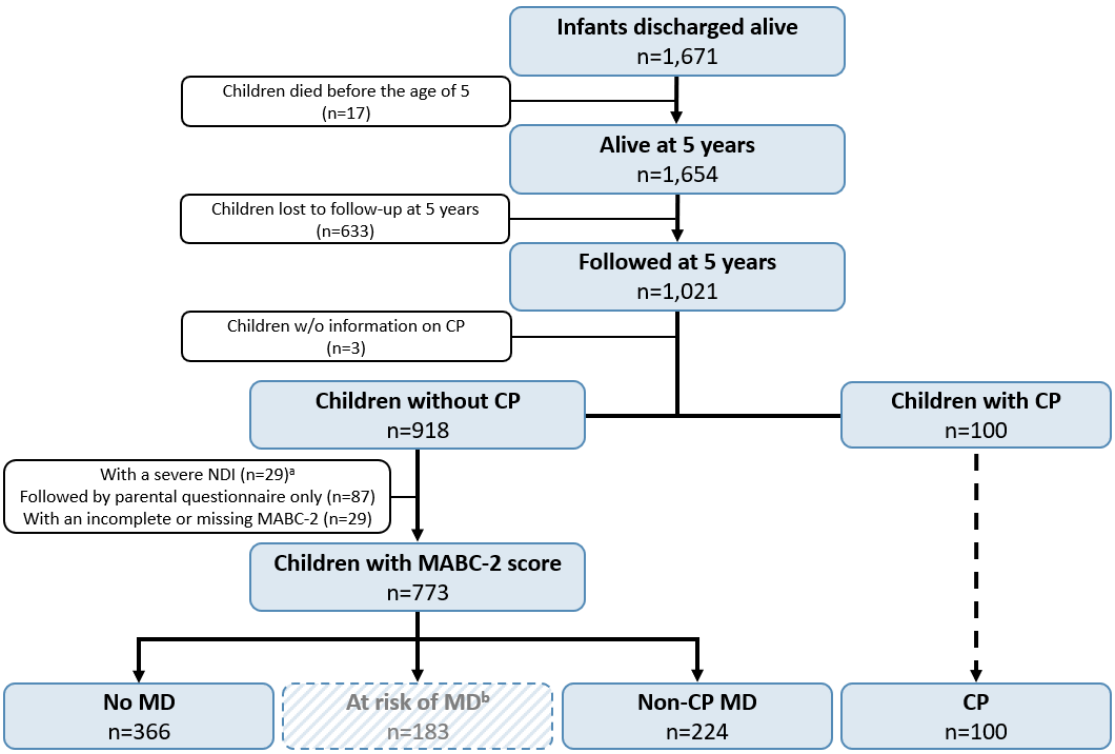
The authors have no conflicts of interest relevant to this article to disclose.

Consent statement:

Parents gave their written informed consent to participating in the study prior to any data collection.

Figure 1. Flowchart of the study population selection from the 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. MD, movement difficulties. No MD (MABC-2 >15th percentile); at risk of MD (6th to 15th percentile); non-CP MD (≤5th percentile).

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

	No MD		Non-CP MD		CP	
	N	%	N	%	N	%
Sociodemographic characteristics						
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**
Perinatal characteristics						
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**
Neonatal characteristics						
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**
Country (region)						
Belgium (Flanders)	18	**5.3**	12	**5.0**	15	**13.7**
Denmark (Eastern Region)	24	**7.0**	9	**3.6**	2	**1.5**
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**

Abbreviations: 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.

Values are weighted frequencies (Ns 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.

[a]Antepartum hemorrhage after week 20.

[b]Defined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.

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 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]	**RRR** [95% CI]
Sociodemographic factors								
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]
Perinatal factors								
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]
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]

Abbreviations: 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.

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.

[a]Defined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.

Supplemental tables:

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

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

3/ 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.

4/ 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.

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		
	N	%	N	%	
	1,021		633		*p-value*[a]
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**	
Missing	*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**	
Missing	*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**	
Missing	*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**	
Missing	*0*	***0.0***	*0*	***0.0***	
Small for gestational age					*0.031*
<3rd percentile	157	**15.4**	73	**11.5**	
3-9th percentile	82	**8.0**	45	**7.1**	
≥10th percentile	782	**76.6**	515	**81.4**	
Missing	*0*	***0.0***	*0*	***0.0***	
Child sex					*0.83*
Female	489	**47.9**	296	**46.8**	
Male	532	**52.1**	337	**53.2**	
Missing	*0*	***0.0***	*0*	***0.0***	
Multiple birth					*0.41*
Singleton	733	**71.8**	469	**74.1**	
Multiple	288	**28.2**	164	**25.9**	
Missing	*0*	***0.0***	*0*	***0.0***	
Congenital anomaly					*0.23*
No	936	**91.7**	583	**92.1**	
Yes	85	**8.3**	50	**7.9**	
Missing	*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**	
Missing	*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**	
Missing	*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**	
Missing	*20*	***2.0***	*32*	***5.1***	
Global					
Followed-up at 2 years of age					*<0.001*
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**	
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).

[a]P-values from Wald test of logistic regressions adjusted on country and taking into consideration clustering within multiple pairs.

[b]Included intraventricular hemorrhage grade III/IV, cystic periventricular leukomalacia, retinopathy of prematurity stage III or more, and surgical necrotizing enterocolitis.

[c]Defined 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.

[a]Included intraventricular hemorrhage grade III/IV, cystic periventricular leukomalacia, retinopathy of prematurity stage III or more, and surgical necrotizing enterocolitis.

[b]Defined 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	CP	Non-CP MD	CP	Non-CP MD	CP
	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	**2.36** [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]
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]						
<3rd 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]
3rd-9th 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]
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.

[a]Defined 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			
	Unadjusted	Adjusted for all sociodemographic 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]	**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]
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]	**1.57** [0.55-4.44]	**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]	**2.37** [1.22-4.63]	**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]	**0.80** [0.40-1.61]	**0.85** [0.41-1.77]	**0.78** [0.34-1.77]
SGA [≥10th percentile]								
<3rd 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]	**1.12** [0.48-2.60]	**1.77** [0.63-5.00]	**1.84** [0.63-5.41]
3rd-9th 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]	**1.02** [0.36-2.88]	**1.49** [0.51-4.32]	**1.36** [0.41-4.52]
Apgar <7 [No]								
Yes	**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]	**2.92** [1.60-5.34]	**2.35** [1.25-4.43]	**2.05** [1.00-4.20]
Child sex [Female]								

Male	**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]	**2.76** [1.59-4.78]	**2.84** [1.60-5.04]	**3.76** [1.96-7.22]
Multiple birth [Singleton]								
Multiple	**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]	**0.75** [0.42-1.36]	**0.97** [0.51-1.86]	**0.72** [0.34-1.51]
Delivery in a level 3 maternity unit [Yes]								
No	**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]	**1.95** [0.95-3.99]	**1.48** [0.65-3.36]	**1.42** [0.62-3.26]
Antepartum hemorrhage after week 20 [No]								
Yes	**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]	**1.59** [0.85-2.99]	**1.24** [0.63-2.44]	**0.68** [0.29-1.63]
PROM [No]								
Yes	**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]	**0.84** [0.44-1.62]	**0.94** [0.47-1.91]	**0.67** [0.31-1.46]
Preeclampsia/eclampsia/HELLP [No]								
Yes	**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]	**1.06** [0.42-2.65]	**0.98** [0.31-3.10]	**0.60** [0.16-2.22]
Antenatal corticosteroids [Yes]								
No	**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]	**2.18** [1.11-4.31]	**2.15** [1.00-4.61]	**1.41** [0.58-3.42]
Congenital anomaly [No]								
Yes	**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]	**1.80** [0.68-4.76]	**1.99** [0.68-5.83]	**1.26** [0.40-3.95]
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.

[a]Defined as supplemental oxygen and/or ventilatory support (continuous positive airway pressure or mechanical ventilation) at 36 weeks' postmenstrual age.