[Original article: 3 tables; 0 figures; 2 online tables]

**Minor neurological dysfunction and associations with motor function, general cognitive abilities, and behaviour in children born extremely preterm**

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**PUBLICATION DATA**

Accepted for publication 00th Month 2018.

Published online 00th Month 2018.

**ABBREVIATIONS**

MABC-2 Movement Assessment Battery for Children, Second Edition

MND Minor neurological dysfunction

SDQ Strengths and Difficulties Questionnaire

WISC-IV Wechsler Intelligence Scale for Children, Fourth Edition

[Abstract]

**AIM** To study the prevalence of minor neurological dysfunction (MND) at 6 years of age in a cohort of children born extremely preterm without cerebral palsy (CP) and to investigate associations with motor function, cognitive abilities, and behaviour.

**METHOD** This study assessed 80 children born at less than 27 weeks of gestation and 90 children born at term age between 2004 and 2007 at a mean age of 6 years 6 months. The assessments included a simplified version of the Touwen Infant Neurological Examination, the Movement Assessment Battery for Children, Second Edition (MABC-2), Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV), the Strengths and Difficulties Questionnaire (SDQ), and the parent version of the Five to Fifteen questionnaire.

**RESULTS** Fifty-one of the preterm children had normal neurology, 23 had simple MND, and six had complex MND compared with 88 who had normal neurology and two simple MND in the term-born group (*p*<0.001). There were significant differences between the children with normal neurology and MND in the preterm group in MABC-2-assessed motor function (*p*<0.001), general cognitive abilities with WISC-IV (*p*=0.005), and SDQ overall behavioural problems and peer problems reported by the parents (*p*=0.02 and *p*=0.003 respectively). SDQ teacher-reported overall behavioural and hyperactivity problems were significant between children with normal and simple MND (*p*=0.04 and *p*=0.02).

**INTERPRETATION** Children born extremely preterm, in the absence of CP, are at risk of MND and this is associated with motor function, cognitive ability, and behaviour.

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DOI: 10.1111/dmcn.xxxxx

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*Developmental Medicine & Child Neurology* 2018, 60: 000–000

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**What this paper adds**

* Extremely preterm birth carries a risk of minor neurological dysfunction (MND).
* MND in children born extremely preterm is associated with impaired motor function and cognitive abilities, and behavioural problems.
* Male sex is associated with MND in children born extremely preterm.

[Main text]

Most children born very (<32wks of gestation) and extremely (<28wks of gestation) preterm nowadays regularly survive without developing major neuromotor impairment (cerebral palsy, CP).1 However, these children are still at high risk of developing a range of neurodevelopmental impairments, including cognitive and behavioural difficulties,2–4 and a large proportion of those who survive without CP will develop subtle neurological impairments,5–8 which may affect their daily activities.

The concept of minor neurological dysfunction (MND) can be useful when describing neurological impairments in children who do not develop CP but still have some neuromotor impairment. MND is not a classical neurological diagnosis, but a description of a child’s neurological profile, which describes difficulties with posture, muscle tone regulation, balance, mildly abnormal reflexes, coordination, and cranial nerve function.9 It can be classified as simple MND or complex MND, depending on the number of dysfunctional domains. The prevalence of MND has been described in the typically developing population10–12 and the most common form, simple MND, has little clinical relevance whereas complex MND may be associated with impaired cognitive abilities and motor function, and behaviour problems.9–11,13 MND has also been studied in the context of prematurity and neonatal complications such as brain injury,5,14–16 which is common in children born extremely preterm. Studies have also indicated that MND can be associated with learning, cognitive, and motor problems in children born preterm.5–7,14

Although there is some information available on MND for children born preterm and, to a limited extent, those born very preterm, associations with cognitive abilities, behaviour, and everyday motor activities have not yet been reported in the same study for extremely preterm children. The association between MND and development in other domains may be useful for identifying children at risk of long-term neurodevelopmental problems.

The aims of our study were (1) to investigate the prevalence of MND in a cohort of children born extremely preterm and compare this with term-born children at a mean age of 6 years 6 months, (2) to investigate associations between MND and motor function, general cognitive abilities, and behaviour in the preterm group, and (3) to explore associations between MND and parental reports of the child’s difficulties with daily motor activities in the preterm group. We hypothesized that (1) the prevalence of MND was higher in the extremely preterm group than the comparison group and (2) that children with MND in the preterm group also had more impairments in other investigated developmental domains.

**METHOD**

**Participants**

This prospective cohort study included 118 children who were born extremely preterm (before 27 weeks of gestation) in Stockholm, Sweden, between 1 January 2004 and 31 March 2007. The participants were a subgroup of the national Extremely Preterm Infants in Sweden Study (EXPRESS). The children were examined with neonatal cranial ultrasound for intraventricular haemorrhage and periventricular leukomalacia during their hospital stay in the neonatal period.

The children were invited for follow-up at a mean age of 6 years 6 months. One child with trisomy 21, two with congenital cytomegalovirus infection, and two with congenital malformations were excluded from the sample. Seventeen of the children eligible for follow-up at age 6 years 6 months declined participation and three had moved away, leaving 93 (80%) participants born preterm (Table SI, online supporting information). Ninety-six term-born children recruited from the Swedish Medical Birth Registry, selected for age, postcode, sex, and maternal country of origin, served as a comparison group. Parental educational level was recorded; above high-school level was considered a high level of education.

The regional ethics committee in Stockholm approved the study and parental written informed consent was obtained for all participants.

**Outcome measures**

The assessors were blinded to whether the child was born at term or preterm.

Neurological profile was assessed with a simplified version of the Touwen Infant Neurological Examination17 and included the evaluation of four domains: reflexes, nerve function of the face and eyes, posture and muscle tone, and coordination and balance. The findings were classified on the basis of the number of dysfunctional domains, as normal neurology, simple MND (one or two domains abnormal), or complex MND (more than two domains abnormal).17

CP was diagnosed on the basis of the criteria of the Surveillance of Cerebral Palsy in Europe Working Group.18

The Movement Assessment Battery for Children, Second Edition (MABC-2)19 was used to assess motor function. In the MABC-2, there are three scales; for each of the three scales (manual dexterity, ball skills, and balance) a standard score is calculated, and a total score can be derived by adding the scores from each subscale. For each scale and the total test score, centiles can be derived. Scores no more than the 15th centile are indicative of borderline motor problems, and scores no more than the 5th centile indicate definite motor problems.

The parent version of the Five to Fifteen questionnaire 20 comprises 181 questions that identify difficulties in fine motor skills, gross motor skills, executive functions, perception, memory, language, learning, social skills, and behavioural problems. There are norms for the Scandinavian population, and the questionnaire has been shown to have good reliability and validity.20 This study only used the responses for fine and gross motor skills, with a cut-off above the 90th centile indicating clinically relevant problems.20 We used this information to assess whether MND would be associated with parent-rated everyday motor function.

General cognitive abilities were assessed with the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV).21 Full-scale intelligence quotient (mean 100, SD 15), working memory, verbal comprehension, perceptual reasoning, and speed of information processing composite scores were used in this study.

Behaviour was evaluated with the parent and teacher report of the Strengths and Difficulties Questionnaire (SDQ).22 The SDQ contains four scales: emotional symptoms (normal range for parents 0–3, teacher 0–4), conduct problems (0–2), hyperactivity/attention (0–5), and peer relationship problems (0–2, 0–3). A summarized score of 0 to 13 is considered normal, 14 to 16 borderline, and 17 to 40 abnormal in the parent version; 0 to 11 is considered normal, 12 to 16 borderline, and 16 to 40 abnormal in the teacher version. Prosocial behaviour has a normal score of 6 to 10.

**Statistical analysis**

Data were analysed using SPSS 22.0 (SPSS Inc, Chicago, IL, USA). The Student’s *t*-test, Mann–Whitney *U* test, and Kruskal–Wallis H test were used, as appropriate, to identify differences between the groups in continuous data. Kendall’s tau-b, the *χ*2 test, Fisher’s exact test, or the *χ*2 for trendwere used, as appropriate, for categorical outcomes, to investigate associations between neurological classification groups (normal, simple MND, complex MND). Three separate multiple linear regressions were performed to investigate associations between neurological profiles and motor skills, cognition, and behaviour, while controlling for relevant clinical variables. The MABC-2 total score, full-scale intelligence quotient, and SDQ summarized scores were entered into the regression analyses as dependent variables. The independent variable was ‘neurology profile’ (with ordinal classification, normal, simple MND, complex MND). Other variables were included in the final regression models if there was evidence from a clinical perspective that they might be associated with the dependent variables, or they were variables that were significant in a univariate test with a *p* value less than 0.1. Assumptions about the absence of multicollinearity problems, the Durbin-Watson value for independence of observations, equal variance, outliers, normality of residuals, and linearity were met in the regression analyses. The statistical significance level was set at a two-sided *p* value of less than 0.05.

**RESULTS**

Nine extremely preterm children were diagnosed with CP and were therefore excluded from further analyses (Table SI, online supporting information); four of the remaining children born extremely preterm and six of the term-born children did not complete the neurological examination. The drop-out analyses are presented in Table SI, and the neonatal characteristics of the remaining 80 preterm and 90 term children in the sample are presented in Table I.

One child who underwent a neurological examination in the preterm group did not complete the MABC-2 and the WISC-IV assessments, two did not complete the M-ABC assessment, and five children born preterm did not complete the WISC-IV assessment.

The response rate for the questionnaires in the group of 80 children born preterm was SDQ parents 78 (98%), SDQ teacher 50 (63%), and Five to Fifteen questionnaire 64 (80%). In the term group it was SDQ parents 90 (100%), SDQ teacher 66 (73%), and Five to Fifteen questionnaire 88 (98%).

**Prevalence and characteristics of MND**

MND was significantly more prevalent in the preterm group than in the term-born group. Fifty-one (64%) of the participants born preterm had normal neurology, 23 (28.7%) had simple MND, and six (7.5%) had complex MND, compared with 88 (98%), two (2%), and 0 respectively, in the term group (*p*<0.001).

Among the preterm children with simple MND, distributions of dysfunctional domains were as follows: five out of 23 within the domain ‘reflexes’, seven out of 23 in the domain ‘posture and muscle tone’, and 14 out of 23 within ‘coordination and balance’. In the complex MND group, six out of six within ‘posture and muscle tone’, two out of six in the cluster ‘reflexes’, six out of six for the cluster ‘coordination and balance’, and five out of six within ‘cranial nerve function’.

In the extremely preterm group, male sex was related to the prevalence and degree of MND (*p*=0.047) (Table I). Parental education was not associated with MND (mother *p*=1.00, father *p*=0.60). Since there were only two children with simple MND in the term-born group, no further analyses were possible within the term-born group between children with simple MND and normal neurology.

There were significant differences between children born extremely preterm and the term-born comparison group in motor function with M-ABC, parent-reported motor problems, cognitive abilities, and behaviour problems reported by the parents (Table SII, online supporting information).

**MND and association with motor function**

Children born extremely preterm with either simple MND or complex MND had significantly lower MABC-2 total scores (*p*<0.001), and lower scores in all subscales, than children born preterm with normal neurology (significant *p* values for simple MND were manual dexterity [*p*<0.001], aiming and catching [*p*=0.006], balance [*p*<0.001]; and for complex MND they were manual dexterity [*p*<0.001], aiming and catching [*p*=0.007], and balance *p*<0.001; Table II).

In the preterm group, children who scored below the 15th and 5th centiles were nine and two in the normal neurology group, 14 and 13 in the simple MND group, and six children in the complex MND group. One term-born child with normal neurology scored below the 15th centile.

After adjusting for confounders, MND was still a significant predictor of motor function (MABC-2) in a multiple linear regression (*F*4,69=10.2, *p*<0.001, *r*2=0.37; the model explains a large amount of variance) (Table III).

**MND and association with everyday motor function**

The Five to Fifteen questionnaire results showed that there was an association in the preterm group between the presence of relevant gross motor difficulties reported by the parents and MND (*p*=0.009; Table II), but no significant associations between MND and fine motor difficulties (*p*=0.09). Parents reported that four of the 87 term-born children with normal neurology had relevant gross motor problems, three of 88 had fine motor problems, and one child had both.

**MND and association with cognitive abilities**

The WISC-IV full-scale intelligence quotient (*p*=0.001), processing speed (*p*=0.03), perceptual reasoning (*p*=0.01), working memory (*p*=0.02), and verbal comprehension (*p*=0.01) scores were significantly lower in the complex MND group than for those with normal neurology. MND was a predictor for WISC-IV full-scale intelligence quotient in a multiple regression model, even after adjusting for confounders (*F*4,66=4.6, *p*=0.003, *r*2=0.21; the model explains a small amount of variance; Table III).

**MND and associations with behaviour**

We observed significant differences between the groups in SDQ overall behaviour problems and peer problems reported by the parents (Table II). A significant difference was seen in overall behaviour problems (*p*=0.04) and peer problems (*p*=0.001) between children with normal neurology and those with complex MND. Peer problems were significantly different between children with simple and complex MND (*p*=0.003) as well as between children with normal neurology and simple MND (*p*=0.007). Behaviour problems were also significantly different between children with normal neurology and simple MND (*p*=0.03). Parents of five out of 50 of the children in the normal neurology group reported overall borderline behaviour problems with SDQ, as did six out of 23 for children in the simple MND group, and two out of five in the complex MND group (*p*=0.03). In a multiple regression model, MND did not predict SDQ overall parent-reported behavioural problems (Table III).

Overall behaviour (*p*=0.04) and hyperactivity (*p*=0.02) problems were also significantly more commonly reported by the teachers for children with simple MND than for those with normal neurology. Only a few teachers (*n*=3) responded to the questionnaire in the complex MND group; therefore, associations between MND and teacher-reported behaviour could not be examined.

**DISCUSSION**

This study explored the prevalence of MND at the age of 6 years 6 months in a cohort of children born extremely preterm, compared with term-born children, and explored associations between MND and motor function and other developmental outcomes, such as general cognitive abilities and behaviour.

Simple and complex MND were much more common in children born preterm than term-born children. In the preterm groups we saw significant differences between those children with normal neurology, and simple and complex MND with performance on the M-ABC, and parent-reported everyday motor skills and general cognitive abilities, as well as behaviour. Coordination and balance problems were the prevalent dysfunctional domains in both groups (simple and complex MND), which is reflected in the parent-reported gross motor problems.

Males born preterm have been shown to be at higher risk of developmental impairments2,23 and to have a higher prevalence of MND than female children born preterm.5,16 Our findings reflect this.

Three separate regression models showed that MND remained the variable that was the strongest predictor of motor function and general cognitive abilities.

The prevalence of MND in term-born populations and relationships with motor function, and general cognitive abilities, has been discussed in previous studies.10,12,13 However, there is still little information available on very and extremely preterm populations. Mikkola et al.,2 who used the full Touwen examination, reported a similar prevalence of MND in their extremely preterm study population, namely 17% with simple and 6% with complex MND. In the EPIPAGE study (using the simplified version of the Touwen examination), in children born preterm before 33 weeks of gestation, the prevalence of simple MND was slightly higher at 52%, and 5% of the children had complex MND.5 The associations between MND and cognitive abilities, motor skills, and behaviour found in our cohort are in line with other studies in less immature populations.5

It has been shown in term-born children and adolescents that attention deficits/hyperactivity are related to MND.11,24 Our findings in a school-aged cohort of children born extremely preterm are similar; significantly more hyperactivity problems on the SDQ teacher version in children born preterm with simple MND were reported compared with those with normal neurology.

It is assumed that MND reflects dysfunction of the nervous system and it has been suggested that the origin of simple MND is either genetic or caused by stress in early postnatal life affecting the monoaminergic system in the brain,9 resulting in non-optimal brain function. Complex MND has been interpreted in the context of inadequate cortico-striato-thalamo-cortical and cerebello-thalamo-cortical circuits in the brain. These are regions that are also involved in cognitive and behaviour development,9–11 and have been shown to be affected in brain injury or altered brain structure in the context of preterm birth. Several studies including very preterm and extremely preterm-born children have shown alterations in several motor pathways and the corpus callosum compared with term-born children.25–27 Cerebellar growth has been shown to be affected in the preterm brain, with smaller volumes and the association not only with motor skills but also with cognition and behavioural processes and cerebellar volumes.28,29 Such alterations in brain development might underlie MND and the associations with other developmental outcomes in the preterm group; this has been indicated by Setänen et al.,16 who showed that complex MND was associated with smaller volumes of thalamus, basal ganglia, and cerebellum.

Parents of children with MND perceived their children to have gross motor problems, including clumsiness, riding a bicycle, and running. This is of clinical importance since it indicates that MND can affect daily activities and may affect school performance. Overall, our findings emphasize the importance of long-term follow-up, which should include systematic and standardized assessments of neurology and motor function, and take parents’ and children’s views into account, even if the children do not develop CP.

The strengths of this study are that our sample was a population-based, followed preterm cohort with a high follow-up rate and matched term-born comparisons. We showed that in children born extremely preterm the prevalence of MND was significantly higher than in term-born participants, and that this has clinically significant implications for everyday motor function, cognitive abilities, and behaviour. There are some limitations of our study. In our term-born comparison group, the expected prevalence of MND was not seen, which might be a true finding or caused by interrater variability. We adjusted for the most common confounders that are known to affect outcome in the regression models; however, it cannot be overlooked that other factors such as microscopic white matter injury might have influenced the results. Further limitations may be that those children who were lost to the study and those who were unable to complete the neurological examination might have had impaired neurodevelopmental outcome, which could introduce some bias. We used a simplified version of the Touwen examination, which excluded three domains (fine manipulative ability, dyskinesia, associated movements) from the original version. This might have influenced the results in terms of prevalence of MND and the association with it and other developmental domains. However, the study by Fily et al.,17 in which the full Touwen examination was compared with the simplified version for a preterm population, showed good agreement between the two approaches; we are therefore confident that neither prevalence of MND in our sample nor associations with other neurodevelopmental domains were significantly affected by using the simplifiedversion.

There is increasing evidence that early intervention can improve motor skills.30 Developing a reliable tool for identification of MND even before preschool age is therefore important; similarly, randomized controlled trials to further examine the effect of early intervention in children born extremely preterm with MND are needed. One randomized controlled trial with an unselected sample of children born preterm allocated to either a motor intervention or a control group found that the motor development over a 5-year period was significantly better in the intervention group than the control group.30 These promising findings need to be replicated in further studies, and, importantly, in children born extremely preterm.

**CONCLUSION**

Even though most children born preterm survive without CP, this study provides further evidence that children born extremely preterm are at higher risk of subtler neurological problems than their peers. Importantly, this has relevance for their daily activities, and is associated with impairment of general cognitive abilitiesand behavioural function.

**ACKNOWLEDGEMENTS**

We especially thank our research nurse Lena Swartling Schlinzig, the Extremely Preterm Infants in Sweden Study (EXPRESS) group, and all the children and their parents for participation in the study. This work was supported by the Swedish Medical Research Council (grant number 523-2011-3981), the regional agreement on medical training and clinical research (grant number ALF-20160227) between Stockholm County Council and Karolinska Institutet, the Marianne and Marcus Wallenberg foundation (grant number 2011.0085), the Swedish Order of Freemasons in Stockholm, the Swedish Medical Society, the Swedish Brain Foundation (grant number FP2014-0135), and Sällskapet Barnavård. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have stated that they had no interest that could be perceived as posing a conflict or bias.

**SUPPLEMENTARY INFORMATION**

The following additional materials may be found online:

**Table SI:** Characteristics of the preterm group.

**Table SII:** Differences in outcomes between preterm and term-born comparison children.

**REFERENCES**

1. Sellier E, Platt MJ, Andersen GL, Krageloh-Mann I, De La Cruz J, Cans C. Decreasing prevalence in cerebral palsy: a multi-site European population-based study, 1980 to 2003. *Dev Med Child Neurol* 2016; **58**: 85–92.
2. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics* 2005; **116**: 1391–400.
3. Serenius F, Källén K, Blennow M, et al. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. *JAMA* 2013; **309**: 1810–20.
4. 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**: 309–15.
5. Arnaud C, Daubisse-Marliac L, White-Koning M, et al. Prevalence and associated factors of minor neuromotor dysfunctions at age 5 years in prematurely born children: the EPIPAGE Study. *Arch Pediatr Adolesc Med* 2007; **161**: 1053–61.
6. 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.
7. Kurpershoek T, Potharst-Sirag ES, Aarnoudse-Moens CS, van Wassenaer-Leemhuis AG. Minor neurological dysfunction in five year old very preterm children is associated with lower processing speed. *Early Hum Dev* 2016; **103**: 55–60.
8. Marlow N, Roberts BL, Cooke RW. Motor skills in extremely low birthweight children at the age of 6 years. *Arch Dis Child* 1989; **64**: 839–47.
9. Hadders-Algra M. Two distinct forms of minor neurological dysfunction: perspectives emerging from a review of data of the Groningen Perinatal Project. *Dev Med Child Neurol* 2002; **44**: 561–71.
10. Kikkert HK, de Jong C, Hadders-Algra M. Minor neurological dysfunction and cognition in 9-year-olds born at term. *Early Hum Dev* 2013; **89**: 263–70.
11. Kikkert HK, de Jong C, van den Heuvel ER, Hadders-Algra M. Minor neurological dysfunction and behaviour in 9-year-old children born at term: evidence for sex dimorphism. *Dev Med Child Neurol* 2013; **55**: 1023–9.
12. van Hoorn JF, Maathuis CG, Peters LH, Hadders-Algra M. Handwriting, visuomotor integration, and neurological condition at school age. *Dev Med Child Neurol* 2010; **52**: 941–7.
13. Peters LH, Maathuis CG, Hadders-Algra M. Limited motor performance and minor neurological dysfunction at school age. *Acta Paediatr* 2011; **100**: 271–8.
14. Potharst ES, van Wassenaer AG, Houtzager BA, van Hus JW, 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.
15. Hadders-Algra M, Heineman KR, Bos AF, Middelburg KJ. The assessment of minor neurological dysfunction in infancy using the Touwen Infant Neurological Examination: strengths and limitations. *Dev Med Child Neurol* 2010; **52**: 87–92.
16. Setänen S, Lehtonen L, Parkkola R, Aho K, Haataja L; PIPARI Study Group. Prediction of neuromotor outcome in infants born preterm at 11 years of age using volumetric neonatal magnetic resonance imaging and neurological examinations. *Dev Med Child Neurol* 2016; **58**: 721–7.
17. Fily A, Truffert P, Ego A, Depoortere MH, Haquin C, Pierrat V. Neurological assessment at five years of age in infants born preterm. *Acta Paediatr* 2003; **92**: 1433–7.
18. 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.
19. Henderson SE, Sugden DA, Barnett AL. Movement assessment battery forChildren—second edition (MABC-2). London: The Psychological Corporation, 2007.
20. Kadesjö B, Janols LO, Korkman M, et al. The FTF (Five to Fifteen): the development of a parent questionnaire for the assessment of ADHD and comorbid conditions. *Eur Child Adolesc Psychiatry* 2004; **13**(Suppl. 3): 3–13.
21. Wechsler D. Wechsler Intelligence Scale For Children (4th edition) (WISC-IV). San Antonio, TX: The Psychological Corporation, 2003.
22. Goodman R. The Strengths and Difficulties Questionnaire: a research note. *J Child Psychol Psychiatry* 1997; **38**: 581–6.
23. Skiöld B, Alexandrou G, Padilla N, Blennow M, Vollmer B, Adén U. Sex differences in outcome and associations with neonatal brain morphology in extremely preterm children. *J Pediatr* 2014; **164**: 1012–8.
24. Batstra L, Neeleman J, Hadders-Algra M. The neurology of learning and behavioural problems in pre-adolescent children. *Acta Psychiatr Scand* 2003; **108**: 92–100.
25. de Kieviet JF, Pouwels PJ, Lafeber HN, Vermeulen RJ, van Elburg RM, Oosterlaan J. A crucial role of altered fractional anisotropy in motor problems of very preterm children. *Eur J Paediatr Neurol* 2014; **18**: 126–33.
26. Groeschel S, Tournier JD, Northam GB, et al. Identification and interpretation of microstructural abnormalities in motor pathways in adolescents born preterm. *Neuroimage* 2014; **87**: 209–19.
27. Grunewaldt KH, Fjørtoft T, Bjuland KJ, et al. Follow-up at age 10 years in ELBW children - functional outcome, brain morphology and results from motor assessments in infancy. *Early Hum Dev* 2014; **90**: 571–8.
28. Limperopoulos C, Soul JS, Gauvreau K, et al. Late gestation cerebellar growth is rapid and impeded by premature birth. *Pediatrics* 2005; **115**: 688–95.
29. Noroozian M. The role of the cerebellum in cognition: beyond coordination in the central nervous system. *Neurol Clin* 2014; **32**: 1081–104.
30. Van Hus J, Jeukens-Visser M, Koldewijn K, et al. Early intervention leads to long-term developmental improvements in very preterm infants, especially infants with bronchopulmonary dysplasia. *Acta Paediatr* 2016; **105**: 773–81.

**Table I:** Neonatal characteristics and cranial ultrasound findings according to minor neurological dysfunction (MND) profile group

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Characteristic | Preterm normal neurology, *n*=51 | Preterm MND 1, *n*=23 | Preterm MND 2, *n*=6 | *p* | Term-born normal, *n*=88 | Term-born MND 1, *n*=2 |
| Median birthweight (range), g | 834 (554–1161) | 773 (600–1109) | 754 (561–917) | 0.61b | 3610 (2850–4515) | 4350 (4095–4605) |
| Median gestational age (range) at birth, wks | 25.5 (23.1–26.6) | 25.5 (23.4–26.6) | 25.3 (24.1–25.6) | 0.55b | 40.0 (37.1–41.6) | 40.4 (41.2–41.5) |
| Male sex, *n* (%) | 23 (45) | 14 (61) | 5 (83) | 0.047a | 53 (60) | 1 (50) |
| Small for gestational age, *n* (%) | 3 (6) | 2 (9) | 1 (17) | 0.37a | — | — |
| Antenatal steroids, *n* (%) | 46 (94) | 22 (96) | 5 (100) | 0.55a | — | — |
| Caesarean delivery, *n* (%) | 19 (39) | 13 (57) | 2 (40) | 0.37a | — | — |
| Postnatal steroids, *n* (%) | 6 (12) | 5 (22) | 1 (20) | 0.34a | — | — |
| Sepsis, *n* (%) | 33 (67)  | 20 (87) | 4 (80) | 0.13a | — | — |
| Necrotizing enterocolitis Bell grade 2–3, *n* (%) | 6 (12) | 2 (9) | 1 (20) | 0.93a | — | — |
| Median time on mechanical ventilation (range), d | 8 (0–43) | 9 (0–50) | 14 (0–55) | 0.89b | — | — |
| Median time on CPAP (range), d | 38 (19–58) | 38 (22–108) | 38 (32–60) | 0.96b | — | — |
| Bronchopulmonary dysplasia, O2 at age 36wks, *n* (%) | 20 (42) | 8 (35) | 4 (80) | 0.43a | — | — |
| Patent ductus arteriosus, ibuprofen treated, *n* (%) | 28 (57) | 17 (74) | 3 (60) | 0.35a | — | — |
| Patent ductus arteriosus, surgical ligation, *n* (%) | 16 (33) | 6 (26) | 1 (20) | 0.45a | — | — |
| Retinopathy of prematurity, laser treated, *n* (%) | 4 (8) | 4 (17) | 1 (20) | 0.23a | — | — |
| Periventricular leukomalacia, *n* | 1 | 1 | 0 | 0.87a | — | — |
| Intraventricular haemorrhage, grade I–II/III–IV, *n* | 18/3 | 7/1 | 1/2 | 0.90c | — | — |

a*χ*2 test for trend. bKruskal–Wallis H. cKendall’s tau-b. CPAP, continuous positive airway pressure.

**Table II:** Motor, cognitive, and behavioural assessment within the preterm group

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Examination | Normal neurology | MND 1 | MND 2 | *p* |
| MABC-2 | *n*=49 | *n*=22 | *n*=6 |  |
| Median total test score (range) | 74 (47–97) | 50 (27–91) | 51 (27–56) | <0.001a |
| Manual dexterity, component score, median (range) | 26 (5–38) | 20 (7–34) | 15 (3–23) | <0.001a |
| Median aiming and catching, component score (range) | 18 (9–27) | 14 (7–27) | 13 (6–19) | 0.002a |
| Median balance, component score (range) | 30 (14–36) | 21 (7–36) | 20 (9–28) | <0.001a |
| FTF parents |  |  |  |  |
| Gross motor problems, *n* (%) | 11/43 (26) | 8/18 (44) | 3/3 (100) | 0.009a |
| Fine motor problems, *n* (%) | 9/41 (22) | 7/17 (41) | 2/4 (50) | 0.09 |
| WISC-IV | *n*=49 | *n*=20 | *n*=5 |  |
| Median FSIQ (range) | 89 (71–120) | 85 (66–108) | 76 (57–81) | 0.005a |
| Median processing speed (range) | 91 (70–128) | 80 (56–109)  | 75 (68–88) | 0.03a |
| Median perceptual reasoning (range) | 94 (71–125) | 90 (67–110) | 84 (71–88) | 0.04a |
| Median working memory (range) | 83 (59–116) | 80 (52–97) | 65 (54–83) | 0.047a |
| Median verbal comprehension (range) | 99 (69–138) | 93 (69–126) | 89 (65–96) | 0.02a |
| SDQ parents | *n*=50 | *n*=23 | *n*=5 |  |
| Median overall raw score (range) | 7 (0–28) | 7 (2–26) | 13 (10–18) | 0.02a |
| Median emotional problems(range) | 1 (0–9) | 2 (0–9) | 3 (0–5) | 0.39 |
| Median conduct problems (range) | 1 (0–7) | 2 (0–7) | 1 (1–2) | 0.07 |
| Median hyperactivity (range) | 2 (0–9) | 3 (0–9) | 4 (3–8) | 0.11 |
| Median peer problems (range) | 1 (0–6) | 0 (0–6) | 4 (4–6) | 0.003a |
| Median prosocial (range) | 9 (4–10) | 8 (5–10) | 8 (6–10) | 0.36 |
| SDQ teacher | *n*=32 | *n*=15 | *n*=3 |  |
| Median overall raw score (range) | 4 (0–20) | 9 (0–21) | — | 0.04a |
| Median emotional problems (range) | 0 (0–9) | 1 (0–7) | — | 0.24 |
| Median conduct problems (range) | 0 (0–5) | 1 (0–4) | — | 0.20 |
| Median hyperactivity (range) | 0 (0–10) | 4 (0–9) | — | 0.02a |
| Median peer problems (range) | 0 (0–4) | 1 (0–5) | — | 0.19 |
| Median prosocial (range) | 9 (3–10) | 7 (1–10) | — | 0.16 |

aSignificant *p* value. MND, minor neurological dysfunction; MABC-2, Movement Assessment Battery for Children, Second Edition; FTF, Five to Fifteen questionnaire; WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition; FSIQ, full-scale intelligence quotient; SDQ, Strengths and Difficulties Questionnaire.

**Table III:** Linear regression analyses within the preterm group exploring the prediction of minor neurological dysfunction (MND) of motor function, overall cognitive abilities, and behaviour controlling for confounders

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | *β* | SE | *t* | *p* | CI of *β* | *r*2 |
| Model 1 (outcome: M-ABC total score) |  |  |  | <0.001 |  | 0.37 |
| MND | −15.70 | 2.62 | −6.00 | <0.001 | −20,92 to −10.48 |  |
| Sex (male) | −3.54 | 3.27 | −1.08 | 0.28 | −10.07 to 2.99 |  |
| Gestational age at birth, wks | −1.96 | 1.85 | −1.06 | 0.29 | −5.65 to 1.73 |  |
| Postnatal steroids | −9.79 | 5.17 | −1.89 | 0.06 | −20.11 to 0.53 |  |
| Model 2 (outcome: WISC FSIQ) |  |  |  | 0.003 |  | 0.21 |
| MND | −8.30 | 2.50 | −3.32 | 0.001 | −13.28 to −3.31 |  |
| Sex (male) | 0.89 | 3.04 | 0.29 | 0.77 | −5.17 to 6.96 |  |
| Gestational age at birth, wks | 1.78 | 1.74 | 1.02 | 0.31 | −1.69 to 5.25 |  |
| Postnatal steroids | −4.46 | 4.71 | −0.95 | 0.35 | −13.87 to 4.94 |  |
| Model 3 (outcome: SDQ total score) |  |  |  | 0.11 |  | 0.08 |
| MND | 2.78 | 1.18 | 2.37 | 0.02 | 0.44 to 5.13 |  |
| Sex (male) | 0.90 | 1.44 | 0.62 | 0.53 | −1.97 to 3.77 |  |
| Gestational age at birth, wks | −0.47 | 1.44 | −0.69 | 0.53 | −1.97 to 3.77 |  |

Model 1: MND, sex, gestational age at birth, and postnatal steroid treatment as independent variables, and Movement Assessment Battery for Children, Second Edition (MABC-2), motor skills scores as dependent variable. Model 2: MND, sex, gestational age at birth, and postnatal steroid treatment as independent variables, and Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV), cognition as dependent variable. Model 3: MND, sex, and gestational age at birth as independent variables, and parent Strengths and Difficulties Questionnaire (SDQ), behaviour scores as dependent variable. *β*, unstandardized regression coefficient; SE, standard error of the mean; CI, confidence interval; *r*2, coefficient of determination; FSIQ, full-scale intelligence quotient.