**Supplemental material: Definitions of patient characteristics and study outcomes**

We extracted the following predefined antenatal, postnatal characteristics and neonatal morbidities from the electronic medical chart: GA, birthweight (BW), small for gestational age (SGA) defined as a BW below the 10th percentile of Dutch reference curves[1], gender, multiple pregnancy, antenatal steroids, mode of delivery, and Apgar score at 5 minutes. Use of (respiratory) medication, such as surfactant, dexamethasone or doxapram, and other respiratory parameters such as duration of mechanical ventilation, total days of supplemental oxygen were also collected. Neonatal comorbidities such as patent ductus arteriosus needing treatment (PDA), necrotizing enterocolitis (NEC) ≥ grade II[2], culture proven sepsis, intraventricular hemorrhage ≥ grade III[3], periventricular leukomalacia[4] and retinopathy of prematurity (ROP) ≥ grade II[5], were collected. Lastly, we calculated the length of NICU stay. Maternal education was used as proxy of social economic status (SES).

Neurodevelopmental outcome was assessed at two- and five-years CA by a dedicated team of neurodevelopmental psychologists, pediatricians and child physiotherapists according to the nationwide follow-up protocol. At two years CA, NDI was defined as having either a Composite Cognitive Score (CCS) and Composite Motor Score (CMS) <-1 standard deviation (SD) (score <85) of the Dutch version of the Bayley Scales of Infant and Toddler Development-III (BSID-III)[6], any grade of cerebral palsy[7, 8], hearing loss despite amplification or severe visual impairment hampering daily activities. At five-years CA, NDI was defined as having either Full Scale Intelligence Quotient (FSIQ) <-1 SD (score<85) of the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III-NL)[9], movement Assessment Battery for Children-2 (mABC) score <-2 SD (≤ 5)[10], complex minor neurological dysfunction (MND) or any grade of CP[7], hearing loss despite amplification or severe visual impairment hampering daily activities. Severe NDI was defined as having a FSIQ<-2 SD (score <70), CP defined as gross motor function classification system (GMFCS)≥2, hearing loss despite amplification or severe visual impairment hampering daily activities. All scores were based on the age corrected for prematurity[11]. Due to a new BSID edition being released during the study period, corrections as previously described were made to enable comparison of the BSID-II to the BSID-III, as well as for the difference between American and Dutch style in reporting[12]. Maternal education status was collected at follow-up and a low level was defined as mothers who had received less than six years of post-elementary schooling[13].

**Supplemental Table 1: Covariates identified using Directed Acyclic Graphs (DAG)**

|  |  |
| --- | --- |
| **Variable name** | **Covariates identified as confounders** |
| Gestational age, weeks | BW, gender and maternal education |
| Birth weight (per 100g) | GA, gender and maternal education |
| Small for GA\*, n(%) | GA, maternal education |
| Male gender, n(%) | No confounders |
| Singleton, n(%) | No confounders |
| Maternal education, low level, n(%)\*\* | No confounders |
| Doxapram, n(%) | BW, GA, duration of IMV |
| Dexamethasone, n(%) | BW, GA, days of supplemental oxygen, duration of IMV |
| Days of supplemental FiO2 | BW, GA, dexamethasone, duration of IMV |
| Duration of IMV, days | BW, GA, dexamethasone, doxapram, days of supplemental oxygen |
| PDA, n(%) | BW, GA, doxapram |
| Sepsis, n(%) | BW, GA, NEC |
| NEC ≥ grade II, n(%) | BW, GA, sepsis |
| ROP ≥ grade II, n(%) | BW, GA, male gender, days of supplemental oxygen |
| IVH ≥ grade III, n(%) | BW, GA, male gender, PDA, sepsis, NEC |
| Duration of NICU stay, days | BW, GA |

\*Defined as a BW below the 10th percentile of Dutch reference curves. \*\*Defined as <6 years of post-elementary education.

*GA*: gestational age. *BW:* birth weight. *IMV:* invasive mechanical ventilation *PDA*: persistent ductus arteriosus needing therapy. *NEC:* necrotizing enterocolitis. *IVH:* intraventricular hemorrhage. *ROP*: retinopathy of prematurity. *NICU:* neonatal intensive care unit.

**Supplemental Table 2**: Patient characteristics loss to follow up at two- and five years corrected age

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Included at two years CA**  **(n=113)** | **Lost to follow-up**  **at two years CA (n=10)** | *P-value* | **Included at five years CA (n=102)** | **Lost to follow-up at five years CA (n=21)** | *P-value* |
| Gestational agea, weeks | 26.3 (25.4, 27.5) | 27.6 (26.2, 28.3) | 0.05 | 26.4 (25.6, 27.6) | 26.0 (25.3, 28.3) | 0.81 |
| Birth weighta, grams | 830 (725, 975) | 920 (820, 1160) | 0.06 | 845 (725, 980) | 820 (775, 1048) | 0.59 |
| Small for GA\*, n(%) | 21 (18.6) | 2 (20.0) | 0.91 | 21 (20.6) | 2 (9.5) | 0.24 |
| Male gender, n(%) | 67 (59.3) | 8 (80.0) | 0.20 | 64 (62.7) | 11 (52.4) | 0.38 |
| Singleton, n(%) | 83 (73.5) | 5 (50.0) | 0.12 | 73 (71.6) | 15 (71.4) | 0.99 |
| Antenatal steroids, n(%) | 101 (89.4) (n=107) | 9 (90) (n=9) | 0.47 | 90 (88.2) (n=96) | 20 (95.2) (n=20) | 0.25 |
| Caesarean section, n(%) | 46 (40.7) | 4 (40.0) | 0.97 | 40 (39.2) | 10 (47.6) | 0.48 |
| Apgar score at 5 minutesa | 8 (6, 9) (n=111) | 6 (6, 8) | 0.04 | 8 (7, 9) (n=100) | 7 (5, 8) | 0.09 |
| Surfactant, n(%) | 76 (67.3) | 6 (60.0) | 0.64 | 72 (70.6) | 10 (47.6) | 0.04 |
| Caffeine, n(%) | 112 (99.1) | 10 (100.0) | 0.77 | 101 (99.0) | 21 (100.0) | 0.65 |
| Doxapram, n(%) | 42 (37.2) | 4 (40.0) | 0.82 | 36 (35.3) | 10 (47.6) | 0.33 |
| Dexamethasone, n(%) | 19 (16.8) | 1 (10.0) | 0.58 | 20 (19.6) | 0 (0) | 0.03 |
| Days of supplemental oxygena | 54.0 (40.5, 72.5) (n=97) | 50.5 (39.0, 76.0) (n=8) | 0.83 | 54.0 (44.0, 75.0) (n=87) | 50.5 (35.3, 67.3) (n=18) | 0.21 |
| Duration of IMV, daysa | 4.5 (1.0, 11.7) | 3.2 (0.9, 7.6) | 0.45 | 4.1 (1.0, 11.6) | 5.7 (0.8, 8.3) | 0.82 |
| PDA, n(%) | 75 (66.4) | 2 (20.0) | <0.01 | 56 (54.9) | 6 (28.6) | 0.01 |
| Sepsis, n(%) | 62 (54.9) | 0 (0) | <0.01 | 56 (54.9) | 6 (28.6) | 0.03 |
| NEC ≥ grade II, n(%) | 16 (14.1) | 1 (10.0) | 0.77 | 16 (15.7) | 1 (4.8) | 0.33 |
| IVH ≥ grade III, n(%) | 10 (8.9) | 1 (10.0) | 0.57 | 11 (10.8) | 0 (0) | 0.29 |
| ROP≥ grade II, n(%) | 28 (24.8) (n=111) | 1 (10.0) | 0.77 | 28 (24.5) (n=100) | 4 (19.1) | 0.73 |
| PVL, n(%) | 2 (1.8) | 0 (0) | 0.67 | 1 (1.0) | 1 (4.8) | 0.21 |
| Duration of NICU staya, days | 59.5 (43.0, 86.0) | 46.0 (29.0, 53.3) | 0.06 | 59.0 (43.0, 85.0) (n=101) | 53.0 (35.3, 67.3) | 0.57 |

aReported as median (interquartile range)

\*Defined as a BW below the 10th percentile of Dutch reference curves.

*PMA: postmenstrual age. CA: corrected age. BPD:* bronchopulmonary dysplasia. *GA*: gestational age. IMV*:* invasive mechanical ventilation *PDA*: persistent ductus arteriosus needing therapy. *NEC:* necrotizing enterocolitis. *IVH:* intraventricular hemorrhage. *ROP*: retinopathy of prematurity. PVL*:* periventricular leukomalacia. *NICU:* neonatal intensive care unit.

**Supplemental Table 3: Complete case analysis of risk factors for NDI at two years CA in infants with established BPD**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **Two years CA** | | | | | |
|  | *OR* | *95% CI* | *P-value* | *aOR* | *95% CI* | *P-value* |
| Gestational age, weeksa | 0.78 | 0.57 – 1.06 | 0.13 | 1.00^ | 0.67 – 1.51 | 0.97 |
| Birth weight, gramsa | 0.69b | 0.44 – 0.83 | <0.01 | 0.69b^ | 0.49 – 0.93 | 0.02 |
| Small for GA\*, n(%) | 3.30 | 1.23 – 8.98 | 0.01 | 5.72^ | 1.50 – 24.6 | 0.01 |
| Male gender, n(%) | 2.07 | 0.89 – 5.10 | 0.10 | - | - | - |
| Singleton, n(%) | 0.95 | 0.39 – 2.47 | 0.92 | - | - | - |
| Maternal education, low level, n(%)\*\* | 1.22 | 0.41 – 3.41 | 0.71 | - | - | - |
| Doxapram, n(%) | 1.70 | 0.73 – 3.94 | 0.21 | 1.04^ | 0.35 – 3.02 | 0.94 |
| Dexamethasone, n(%) | 5.63 | 2.01 – 16.9 | <0.01 | 2.40^ | 0.64 – 9.14 | 0.19 |
| Days of supplemental FiO2a | 1.01 | 0.99 – 1.03 | 0.12 | 1.00^ | 0.98 – 1.02 | 0.88 |
| Duration of IMV, daysa | 1.07 | 1.02 – 1.13 | 0.02 | 1.00^ | 0.98 – 1.02 | 0.99 |
| PDA, n(%) | 1.13 | 0.47 – 2.81 | 0.79 | 1.17^ | 0.31 – 2.10 | 0.83 |
| Sepsis, n(%) | 1.38 | 0.61 – 3.23 | 0.44 | 1.19^ | 0.49 – 2.90 | 0.70 |
| NEC ≥ grade II, n(%) | 1.47 | 0.46 – 4.36 | 0.50 | 1.09^ | 0.31 – 3.50 | 0.90 |
| ROP ≥ grade II, n(%) | 1.81 | 0.72 – 4.50 | 0.20 | 1.35^ | 0.37 – 5.26 | 0.66 |
| IVH ≥ grade III, n(%) | 4.00 | 1.06 – 16.7 | 0.04 | 4.10^ | 0.94 – 20.3 | 0.07 |
| Duration of NICU stay, daysa | 1.01 | 0.99 – 1.02 | 0.20 | 1.00^ | 0.98 – 1.02 | 0.92 |

aReported as median (interquartile range). bLogistic regression performed per 100 grams. OR odds ratio. CI confidence interval. aOR adjusted odds ratio.

\*Defined as a BW below the 10th percentile of Dutch reference curves. \*\*Defined as <6 years of post-elementary education.

*NDI: neurodevelopmental impairment. CA: corrected age. BPD: bronchopulmonary dysplasia. GA: gestational age. IMV: invasive mechanical ventilation PDA: persistent ductus arteriosus needing therapy. NEC: necrotizing enterocolitis. IVH: intraventricular hemorrhage. ROP: retinopathy of prematurity. NICU: neonatal intensive care unit.* Neurodevelopmental impairment (NDI) is defined as at two years CA defined as having a composite cognitive score (CCS) < 85 (-1SD), composite motor score (CMS) < 85 (-1SD), cerebral palsy (CP) defined as gross motor function classification system ≥ 2, hearing loss despite amplification and/or severe visual impairment hampering daily activities.

^Specific adjustments per variable can be found in Table 1 online

**Supplemental Table 4: Sensitivity analysis using severe NDI definition at five years CA**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **Five years CA** | |  |  |  |  |  |  |
|  | **Severe NDI**  (n= 16) | **No severe NDI** (n=78) | *OR* | *95% CI* | *P-value* | *aOR* | *95% CI* | *P-value* |
| Gestational age, weeksa | 26.1 (25.0, 27.1) | 26.9 (25.7, 27.9) | 0.85 | 0.61 – 1.20 | 0.35 | 0.92 | 0.62 – 1.36 | 0.68 |
| Birth weight (g)a | 788 (646, 889) | 863 (733, 1011) | 0.86 | 0.69 – 1.09 | 0.21 | 0.86 | 0.68 – 1.08 | 0.18 |
| Small for GA\*,n(%) | 5 (31.3) | 16 (20.5) | 1.07 | 0.37 – 3.13 | 0.90 | 1.10 | 0.36 – 3.43 | 0.85 |
| Male gender, n(%) | 10 (62.5) | 48 (61.5) | 1.31 | 0.48 – 3.56 | 0.59 | - | - | - |
| Singleton, n(%) | 10 (62.5) | 57 (73.1) | 0.65 | 0.23 – 1.85 | 0.41 | - | - | - |
| Maternal education, low level\*\*, n(%) | 2 (29) (n=7) | 22 (28.2) (n=65) | 0.90 | 0.28 – 2.90 | 0.86 | - | - | - |
| Doxapram, n(%) | 6 (37.5) | 24 (30.8) | 1.54 | 0.61 – 3.87 | 0.35 | 1.01 | 0.28 – 3.71 | 0.77 |
| Dexamethasone, n(%) | 5 (31.3) | 14 (17.9) | 1.21 | 0.42 – 3.54 | 0.84 | 0.48 | 0.17 – 1.96 | 0.33 |
| Days of supplemental FiO2a | 77.5 (49.3, 100.0) | 50.0 (40.0, 66.0) | 1.02 | 1.00 – 1.03 | 0.09 | 1.00 | 0.99 – 1.03 | 0.42 |
| Duration of IMV, daysa | 10.6 (0.3, 18.2) | 3.8 (0.99, 10.2) | 1.04 | 0.99 – 1.09 | 0.11 | 1.04 | 0.97 – 1.11 | 0.23 |
| PDA, n(%) | 9 (56.3) | 54 (69.2) | 0.67 | 0.27 – 1.68 | 0.39 | 0.50 | 0.18 – 1.41 | 0.19 |
| Sepsis, n(%) | 12 (75.0) | 40 (51.3) | 1.13 | 0.47 – 2.73 | 0.77 | 0.90 | 0.35 – 2.31 | 0.82 |
| NEC ≥ grade II, n(%) | 4 (25.0) | 8 (10.3) | 2.59 | 0.80 – 8.38 | 0.11 | 2.51 | 0.72 – 8.74 | 0.15 |
| ROP ≥ grade II, n(%) | 7 (43.8) | 16 (20.5) (n=76) | 1.30 | 0.52 – 3.23 | 0.57 | 0.79 | 0.25 – 2.49 | 0.69 |
| IVH ≥ grade III, n(%) | 5 (31.3) | 5 (6.4) | 4.49 | 1.14 – 17.7 | 0.03 | 5.78 | 1.27 – 26.3 | 0.02 |
| Duration of NICU stay, daysa | 68.5 (47.5, 110.8) | 55.0 (41.0, 72.0) | 1.01 | 1.00 – 1.03 | 0.18 | 1.01^ | 0.99 – 1.02 | 0.42 |

aReported as median (interquartile range). OR odds ratio. aOR adjusted odds ratio. CI confidence interval.

\*Defined as a BW below the 10th percentile of Dutch reference curves. \*\*Defined as <6 years of post-elementary education

CA: corrected age. BPD: bronchopulmonary dysplasia. GA: gestational age. IMV: invasive mechanical ventilation PDA: persistent ductus arteriosus needing therapy. NEC: necrotizing enterocolitis. IVH: intraventricular hemorrhage. ROP: retinopathy of prematurity. NICU: neonatal intensive care unit.

Severe neurodevelopmental impairment at five years CA defined as having a full scale Intelligence Quotient (IQ) < 70 (-2SD), gross motor function classification system ≥2, hearing loss despite amplification and/or severe visual impairment hampering daily activities.

^Specific adjustments per variable can be found in Table 1 online

**Supplemental Table 5: Complete case analysis of risk factors for NDI at five years CA in infants with established BPD**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **Five years CA** | | | | | |
|  | *OR* | *95% CI* | *P value* | *aOR* | *95% CI* | *P value* |
| Gestational age, weeksa | 0.63 | 0.45 – 0.86 | 0.01 | 0.74^ | 0.47 – 1.14 | 0.18 |
| Birth weight, gramsa | 0.68b | 0.53 – 0.86 | <0.01 | 0.63b^ | 0.45 – 0.84 | <0.01 |
| Small for GA\*, n(%) | 3.12 | 1.10 – 10.3 | 0.04 | 7.31^ | 1.80 – 36.3 | 0.01 |
| Male gender, n (%) | 2.79 | 1.22 – 6.60 | 0.02 | - | - | - |
| Singleton, n(%) | 1.03 | 0.42 – 2.52 | 0.94 | - | - | - |
| Maternal education, low level, n(%)\*\* | 1.17 | 0.45 – 3.10 | 0.74 | - | - | - |
| Doxapram, n(%) | 1.43 | 0.61 – 3.38 | 0.41 | 0.54^ | 0.16 – 1.65 | 0.29 |
| Dexamethasone, n(%) | 4.00 | 1.33 – 14.9 | 0.02 | 1.91^ | 0.45 – 9.66 | 0.40 |
| Days of supplemental FiO2a | 1.03 | 1.01 – 1.06 | 0.01 | 1.02^ | 0.99 – 1.05 | 0.10 |
| Duration of IMV, daysa | 1.06 | 1.00 – 1.13 | 0.04 | 1.00^ | 0.95 – 1.07 | 0.99 |
| PDA, n(%) | 0.68 | 0.28 – 1.59 | 0.38 | 0.43^ | 0.15 – 1.17 | 0.11 |
| Sepsis, n(%) | 2.18 | 0.97 – 5.00 | 0.06 | 1.52^ | 0.62 – 3.73 | 0.36 |
| NEC ≥ grade II, n(%) | 2.17 | 0.67 – 8.40 | 0.22 | 1.96^ | 0.52 – 8.58 | 0.49 |
| ROP ≥ grade II, n(%) | 4.02 | 1.44 – 13.2 | 0.01 | 1.35^ | 0.37 – 5.26 | 0.66 |
| IVH ≥ grade III, n(%) | 4.02 | 0.96 – 27.3 | 0.09 | 3.78^ | 0.76 – 29.7 | 0.14 |
| Duration of NICU stay, daysa | 1.02 | 1.00 – 1.04 | 0.01 | 1.01 | 0.99 – 1.03 | 0.15 |

aReported as median (interquartile range). bLogistic regression performed per 100 grams. OR odds ratio. CI confidence interval. aOR adjusted odds ratio.

\*Defined as a BW below the 10th percentile of Dutch reference curves. \*\*Defined as <6 years of post-elementary education.

*NDI:* neurodevelopmental impairment*. CA:* corrected age*. BPD*: bronchopulmonary dysplasia*. GA:* gestational age*. IMV:* invasive mechanical ventilation. *PDA:* persistent ductus arteriosus needing therapy*. NEC*: necrotizing enterocolitis*. IVH:* intraventricular hemorrhage. *ROP:* retinopathy of prematurity. *NICU:* neonatal intensive care unit.

Neurodevelopmental impairment at five years CA defined as having a full scale Intelligence Quotient (IQ) < 85 (-1SD), scoring abnormal on the movement assessment battery for children (mABC-2) ≤ 5, complex minor dysfunction or any grade of cerebral palsy, hearing loss despite amplification and/or severe visual impairment hampering daily activities.

^Specific adjustments per variable can be found in Table 1 online

**References**

1. Hoftiezer L, Hof MHP, Dijs-Elsinga J, Hogeveen M, Hukkelhoven C, van Lingen RA. From population reference to national standard: new and improved birthweight charts. Am J Obstet Gynecol. 2019 Apr;220(4):383 e1-83 e17.

2. Neu J, Walker WA. Necrotizing enterocolitis. N Engl J Med. 2011 Jan 20;364(3):255-64.

3. Ment LR, Bada HS, Barnes P, Grant PE, Hirtz D, Papile LA, et al. Practice parameter: neuroimaging of the neonate: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2002 Jun 25;58(12):1726-38.

4. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. Behav Brain Res. 1992 Jul 31;49(1):1-6.

5. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005 Jul;123(7):991-9.

6. Bayley N. Bayley Scales of Infant Development (2nd ed.). 1993.

7. 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 Jan;52(1):87-92.

8. Park EY. Stability of the gross motor function classification system in children with cerebral palsy for two years. BMC Neurol. 2020 May 6;20(1):172.

9. Hendriksen JH P. WPPSI-III-NL Wechsler Preschool and Primary Scale of Intelligence, 3rd edition. Nederlandse bewerking. . Amsterdam, the Netherlands: Pearson Assessment and Information BV. ; 2009.

10. Brown T. Movement Assessment Battery for Children: 2nd Edition (MABC-2). In: Volkmar FR, editor. Encyclopedia of Autism Spectrum Disorders. New York, NY: Springer New York; 2013. p. 1925-39.

11. van Veen S, Aarnoudse-Moens CS, van Kaam AH, Oosterlaan J, van Wassenaer-Leemhuis AG. Consequences of Correcting Intelligence Quotient for Prematurity at Age 5 Years. J Pediatr. 2016 Jun;173:90-5.

12. Katz TA, Vliegenthart RJS, Aarnoudse-Moens CSH, Leemhuis AG, Beuger S, Blok GJ, et al. Severity of Bronchopulmonary Dysplasia and Neurodevelopmental Outcome at 2 and 5 Years Corrected Age. J Pediatr. 2022 Apr;243:40-46 e2.

13. 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 Jul;159(1):79-85.