Two-year neurodevelopmental outcome in children born extremely preterm: the EPI-DAF study

Pauline E van Beek ,[1] Monique Rijken,[2] Lisa Broeders,[3] Hendrik J ter Horst,[4] Corine Koopman-Esseboom,[5] Ellen de Kort,[1] Céleste Laarman,[6] Susanne M Mulder-de Tollenaer,[7] Katerina Steiner,[8] Renate MC Swarte,[9] Elke van Westering-Kroon,[10] S Guid Oei,[11,12] Aleid G Leemhuis,[13] Peter Andriessen ,[14,15] on behalf of the EPI-DAF study group

ABSTRACT

Objective In 2010, the Dutch practice regarding initiation of active treatment in extremely preterm infants was lowered from 25 completed weeks' to 24 completed weeks' gestation. The nationwide Extremely Preterm Infants – Dutch Analysis on Follow-up Study was set up to provide up-to-date data on neurodevelopmental outcome at 2 years' corrected age (CA) after this guideline change.

Design: National cohort study.

Patients All live born infants between $24^{0/7}$ weeks' and $26^{6/7}$ weeks' gestational age who were 2 years' CA in 2018–2020.

Main outcome measure Impairment at 2 years' CA, based on cognitive score (Bayley-III-NL), neurological examination and neurosensory function.

Results 651 of 991 live born infants (66%) survived to 2 years' CA, with data available for 554 (85%). Overall, 62% had no impairment, 29% mild impairment and 9% moderate-to-severe impairment (further defined as neurodevelopmental impairment, NDI). The percentage of survivors with NDI was comparable for infants born at 24 weeks', 25 weeks' and 26 weeks' gestation. After multivariable analysis, severe brain injury and low maternal education were associated with higher odds on NDI. NDI-free survival was 48%, 67% and 75% in neonatal intensive care unit (NICU)-admitted infants at 24, 25 and 26 weeks' gestation, respectively.

Conclusions Lowering the threshold has not been accompanied by a large increase in moderate-to-severely impaired infants. Among live-born and NICU-admitted infants, an increase in NDI-free survival was observed from 24 weeks' to 26 weeks' gestation. This description of a national cohort with high follow-up rates gives an accurate description of the range of outcomes that may occur after extremely preterm birth.

What is already known on this topic?

⇒ Long-term outcomes in neonatal intensive care unit survivors are frequently classified as severe, moderate, mild or no impairment.

⇒ Neurodevelopmental impairment (NDI) includes survivors with moderate-to-severe impairment and is the most commonly reported long-term outcome measure in preterm infants, with higher incidence as gestational age decreases.

⇒ In 2010, the Dutch guideline regarding initiation of active treatment in extremely preterm infants was changed, lowering initiation from 25 weeks' to 24 weeks' gestation.

What this study adds?

⇒ Within a decade after lowering the threshold for supporting active treatment from 25 completed weeks' to 24 completed weeks' gestation, 62% of the extremely preterm survivors did not have any impairment at 2 years' corrected age.

⇒ The change in threshold and subsequent improvement in survival at 24 weeks have not been accompanied by a large increase in survivors with NDI.

⇒ The percentage of survivors with NDI was comparable for children born at 24 weeks', 25 weeks' and 26 weeks' gestation.

INTRODUCTION

The number of preterm deliveries has increased over the last decades, with increasing survival rates in the neonatal intensive care unit (NICU).[1 2] However, improved survival rates raise the concern of an increasing number of surviving preterm infants with adverse long-term outcomes. Preterm born children are known to have a higher risk for neurosensory disabilities and cognitive, motor and behavioural problems later in life, especially at low gestational age (GA).[3–7]

In 2010 a guideline on perinatal treatment of spontaneous extremely preterm birth was implemented in the Netherlands, lowering the threshold for active treatment of preterm infants from 25 completed weeks' to 24 completed weeks' gestation.[8] As such guideline change regarding initiation of active treatment influences antenatal counselling, mortality and neurodevelopmental outcome, we wanted to provide up-to-date data on neurodevelopmental outcome for infants born below 27 weeks' gestation.[9–11] Therefore, the nationwide Extremely Preterm Infants – Dutch Analysis on Follow-up (EPI-DAF) Study was set up, in which neurodevelopmental outcome at 2 years' corrected age (CA) was evaluated over a 3-year period using data from the standardised national follow-up programme.[12]

The first aim of the study was to classify neurodevelopmental outcome as moderate-to-severe, mild or no impairment—using defined categories of cognitive development, neurological examination and neurosensory function—in NICU survivors stratified for completed weeks of gestation. Children with moderate-to-severe impairment were denoted as survivors with neurodevelopmental impairment (NDI). The second aim was to evaluate which perinatal factors influence NDI and to calculate NDI-free survival relative to live-born and NICU-admitted infants for each GA week.

METHODS

Patient population

The EPI-DAF Study included all Dutch live-born infants, born between $24^{0/7}$ weeks' and $26^{6/7}$ weeks' GA, who were 2 years' CA in 2018–2020. Parents signed informed consent during the follow-up visit for research use of the follow-up data and for transport of data to the Netherlands Perinatal Registry (Perined).[13]

Data collection

The registry contains linked population-based information concerning pregnancy, delivery and (re)admissions, as registered by midwives, obstetricians and paediatricians/neonatologists. All 10 NICUs export their data to Perined. Follow-up data were uploaded to Perined and linked to historical perinatal data.

Registry data used for this study included birth weight; GA; small for GA (SGA), lower than tenth percentile based on Hoftiezer;[14] mode of delivery; 5-min Apgar Score; multiplicity; severe necrotising enterocolitis (NEC), defined as pneumatosis intestinalis or perforation; severe brain injury, defined as intraventricular haemorrhage stage 3–4 or severe periventricular leukomalacia grade 2–3. Socioeconomic status (SES) was area-based and assessed using scores defined by the Netherlands Institute for Social and Cultural Research (The Hague, Netherlands) based on the four-didget postal code at birth, with an average score of 0 and a positive score reflecting higher than average status and a negative score reflecting lower than average status.[15] Low SES was defined as a score <-1, high SES was defined as a score $>+1$.

Follow-up assessment

Follow-up care is part of standardised aftercare in children after very preterm birth according to the national guideline for follow-up including a standardised follow-up protocol, carried out in all 10 Dutch NICUs.[12] In principle, parents attend the follow-up clinic attached to the particular NICU their child has been admitted to. At 2 years' CA, this follow-up programme includes assessments by a trained team consisting of a paediatrician/neonatologist, psychologist and physiotherapist, and comprises medical history taking, a physical and neurological examination, and assessment of mental and psychomotor development with the Dutch version of the Bayley Scales of Infant and Toddler Development (Bayley-III-NL, mean 100 (SD 15)). All psychologists and physiotherapists are trained in assessing their scales of the Bayley-III-NL. Parents are asked to fill out the Child Behavioural Checklist (CBL) to rate internalising, externalising and total behaviour problems (mean 50 (SD 10), higher scores indicate more behavioural problems).[16] Neurological examination was performed to determine cerebral palsy (CP), which was graded using the five levels defined in the Gross Motor Function Classification System (GMFCS), from 1 for minimal impairment to 5 for severe impairment with dependence on caretakers for most daily activities.[17] A combination of medical history and results of the assessment was used to rate hearing and vision status. Information on maternal education was collected during follow-up and classified as low, middle or high.[18]

Outcome evaluation

Outcome was classified as moderate-to-severe, mild or no impairment, using defined categories of cognitive development, neurological examination and neurosensory function.[4 5 10 19] The entity 'neurodevelopmental impairment' (NDI) was considered in children with a moderate-to-severe impairment. Moderate-to-severe impairment (ie, NDI) included a Bayley-III-NL cognitive composite score <-2 SD, CP (GMFCS level 2–5), functionally impaired vision or blindness, or hearing loss requiring aids or severe sensorineural hearing loss despite aids. Mild impairment included a Bayley-III-NL cognitive composite score between -1 SD and -2 SD, abnormal neurological examination with abnormal neurological signs but with minimal functioning implications (GMFCS 1), mild visual problems (squints or refractive errors) or mild hearing loss (not sufficient to require aids). If no Bayley-III-NL could be performed, the attending neonatologist and psychologist were asked to assess an estimate of cognitive development (no delay, 3–6 months delay or more than 6 months' delay), corresponding with an impairment of none, mild or moderate-to-severe. Outcome classification was based on the worst determinant in either one of the categories. If children did not visit the neonatal follow-up clinic, but a rehabilitation clinic instead due to severe neurodevelopmental problems, they were included in the study classified as moderate-to-severe impairment.

Although cognitive impairments surpass rates of CP and neurosensory impairment, the quality of motor function and behavioural outcome may also have a significant influence on later impairment.[19 20] Therefore, outcome was also evaluated including motor development and behavioural outcome in all children in which these scores were available. Motor impairment was scored as moderate-to-severe if the child had a Bayley-III-NL composite motor score <-2 SD, and as mild if the child had a score between -1 SD and -2 SD. Behavioural impairment was scored as moderate-to-severe if one of the composite internalising, externalising or total CBCL T-scores were >2 SD, and as mild if one of the composite scores was between 1 SD and 2 SD.

NDI-free survival was calculated relatively to live-born and NICU-admitted infants.

Statistical analysis

Statistical analysis was performed using R V.3.5.2. Baseline characteristics were compared between GA groups using the one-way analysis of variance or Mann-Whitney U test for continuous variables and using the χ^2 test for categorical variables. Maternal education was imputed for 15% of the children with missing information. Impairment was imputed for all 97 surviving infants who were lost to follow-up. Both variables were imputed using an imputation model containing all baseline characteristics of surviving infants including SES (online supplemental appendix 1) and were imputed using the R multivariate imputation by chained equation package. Outcome measures were compared between GA groups using a χ^2 test. If significant, additional pairwise χ^2 tests were performed. Logistic regression was performed for the presence of NDI (moderate-to-severe impairment), including GA, gender, SGA, NEC, severe brain injury and maternal education in the model. A value of $p<0.05$ was considered statistically significant.

Table 1 Baseline characteristics of all infants born at <27 weeks' GA who reached 2 years' CA in 2018–2020, and separately for infants born at 24 weeks', 25 weeks' and 26 weeks' gestation

	Total	24 weeks	25 weeks	26 weeks	P value
Live born (N)	991	271	297	423	
Died before admission (N (% of live born))	100 (10.1)	59 (21.8)	24 (8.1)	17 (4.0)	
Admitted (N (% of live born))	891 (89.9)	212 (78.2)	273 (91.9)	406 (96.0)	
Died after admission (N (% of admitted))	240 (26.9)	98 (46.2)	68 (24.9)	74 (18.2)	
Survived to 2 years' CA (N (% of admitted))	651 (73.1)	114 (53.7)	205 (75.1)	332 (81.8)	
Follow-up data available (N (% of survived))	554 (85.1)	98 (86.0)	178 (86.8)	278 (83.7)	
Maternal age	30.3 (5.2)	30.7 (5.1)	30.6 (5.2)	30.1 (5.3)	0.437
Birth weight (g)	820 (150)	697 (99)	799 (120)	876 (154)	<0.001*
Sex (male)	288 (52.0)	46 (46.9)	93 (52.2)	149 (53.6)	0.524
SGA (<tenth percentile)	99 (17.9)	5 (5.1)	27 (15.2)	67 (24.1)	<0.001*
Caesarean section	185 (33.4)	14 (14.3)	50 (28.1)	121 (43.5)	<0.001*
Multiple birth	154 (27.8)	23 (23.5)	51 (28.7)	80 (28.8)	0.573
5 min Apgar	7(6, 8)	7(5, 8)	7(6, 8)	7(6, 8)	<0.001*
Severe NEC	63 (11.4)	10 (10.2)	21 (11.8)	32 (11.5)	0.919
Severe brain injury	85 (15.3)	15 (15.3)	27 (15.2)	43 (15.5)	0.996
SES					0.251
Low	141 (25.5)	25 (25.5)	46 (25.7)	70 (25.3)	
Intermediate	338 (61.1)	53 (54.1)	111 (62.4)	174 (62.8)	
High	74 (13.4)	20 (20.4)	21 (11.8)	33 (11.9)	
Maternal education					0.100
Low	63 (11.4)	18 (18.4)	14 (7.9)	31 (11.2)	
Intermediate	195 (35.2)	37 (37.8)	58 (32.6)	100 (36.0)	
High	208 (37.5)	30 (30.6)	78 (43.8)	100 (36.0)	
Missing	88 (15.9)	13 (13.3)	28 (15.7)	47 (16.9)	

Birth weight is presented as mean (SD), Apgar score is presented as median (Q1,Q3), other variables are presented as N (%). SGA is defined as birth weight below the tenth percentile. A value of p<0.05 is considered statistically significant. *, significant at 0.05 level
CA, corrected age; GA, gestational age; NEC, necrotising enterocolitis ; SES, socioeconomic status; SGA, small for gestational age.

RESULTS

Study population

Within the study period, 991 infants were live born at 24–26 completed weeks' GA, of whom 891 (90%) were admitted to NICU. Of these, 651 (73%) infants survived and reached 2 years' CA in 2018–2020, of whom 587 (90%) were seen for follow-up at 2 years' CA. Fifty-three children did not return for follow-up, parents of eight children refused follow-up and three children were missed due to COVID-19. Thirty-three children did return, but parents declined consent for registering of follow-up data in Perined, resulting in scientific availability of follow-up data at 2 years' CA of 554 (85%) children. No statistically significant differences were seen in baseline characteristics between surviving children with and without follow-up data available, although 37.5% of the children lost to follow-up were born in families with low SES compared with 25.5% of the children seen for follow-up (online supplemental appendix table 1). Baseline characteristics of all children with follow-up data available are shown in table 1.

Outcome at 2 years' CA

Table 2 shows outcome at 2 years' CA, including cognitive Bayley-III-NL cognitive and motor scores, neurosensory function, the results of the neurological exam and CBCL T-scores. Overall, 62% (95% CI 58% to 66%) had no impairment, 29% (95% CI 25% to 33%) mild impairment and 9% (95% CI 7% to 12%) moderate-to-severe impairment (ie, NDI). Rates of NDI were comparable (around 9%) between children born at 24 weeks', 25 weeks' and 26 weeks' gestation. Detailed information about

the affected domains in children with mild and moderate-to-severe impairment is presented in online supplemental appendix table 2.

When including Bayley-III-NL motor scores in the definition of impairment, the overall rate of children with NDI increased from 9% to 13% (table 2). This increased to 19% when including CBCL T-scores also in the outcome definition.

Multivariable logistic regression showed that severe brain injury and low maternal education were associated with higher odds on NDI (table 3).

NDI-free survival

Figure 1 shows imputed overall outcome for all live-born and NICU-admitted infants. For 24 weeks', 25 weeks' and 26 weeks' live-born infants, 38%, 62% and 72% had NDI-free survival up to 2 years' CA, respectively (p<0.001). For 24 weeks', 25 weeks' and 26 weeks' NICU-admitted infants, 48%, 67% and 75% had NDI-free survival to 2 years' CA, respectively (p<0.001).

DISCUSSION

In 2010, the Dutch practice regarding initiation of active treatment in extremely preterm infants was lowered from 25 completed weeks' to 24 completed weeks' gestation. The EPI-DAF Study evaluated neurodevelopmental outcome at 2 years' CA in extremely preterm children born below 27 weeks' gestation, several years after practice change, and found that the change in intervention threshold has not been accompanied by an increase in moderate-to-severely impaired infants. The main

Table 2 Follow-up results of all 554 infants with follow-up data available born <27 weeks' gestational age (GA) who reached 2 years' corrected age (CA) in 2018–2020, separately for infants born at 24, 25 and 26 weeks' gestation. All follow-up data are presented as N (%), mean (SD) or median (IQR). Impairment rates are presented as % (95% CI). The follow-up programme included a physical and neurological examination and assessment of mental and psychomotor development with the Dutch version of the Bayley Scales of Infant and Toddler Development (Bayley-III-NL, mean 100 (SD 15)). Parents are asked to fill out the Child Behavioral Checklist (CBCL) to rate internalising, externalising and total behaviour problems (mean 50 (SD 10), higher scores indicate more behavioural problems). Neurological examination was performed to determine cerebral palsy (CP), which was graded using the five levels defined in the Gross Motor Function Classification System (GMFCS), from 1 for minimal impairment to 5 for severe impairment with dependence on caretakers for most daily activities. A combination of medical history and results of the assessment was used to rate hearing and vision status. Outcome measures were compared between GA groups using a one-way analysis of variance or Mann-Whitney U-test for continuous variables, depending on distribution, and a χ^2 test for categorical variables. A value of p<0.05 is considered statistically significant

	Total	24 weeks	25 weeks	26 weeks	P value
Follow-up data available	n=554	n=98	n=178	n=278	
Bayley-III-NL cognitive score, N (%) evaluated	497 (89.7)	87 (88.8)	162 (91.0)	248 (89.2)	
Bayley-III-NL cognitive score mean (SD)	96 (14)	94 (12)	95 (15)	97 (13)	0.107
Bayley-III-NL cognitive score median (IQR)	96 (87–105)	96 (87–101)	96 (87–101)	96 (88–105)	0.135
Bayley-III-NL cognitive score 85 or greater	404 (81.3)	70 (80.5)	124 (76.5)	210 (84.7)	0.073
Bayley-III-NL cognitive score 70–84	77 (15.5)	12 (13.8)	30 (18.5)	35 (14.1)	
Bayley-III-NL cognitive score <70	16 (3.2)	5 (5.7)	8 (4.9)	3 (1.2)	
Bayley-III-NL motor score, N (%) evaluated	437 (78.9)	80 (81.6)	135 (75.8)	222 (79.9)	
Bayley-III-NL Bayley motor score mean (SD)	95 (14)	92 (15)	97 (14)	95 (14)	0.037*
Bayley-III-NL Bayley motor score median (IQR)	95 (84–105)	94 (83–101)	98 (87–107)	95 (87–106)	0.053
Bayley-III-NL Bayley motor score 85 or greater	326 (74.6)	51 (63.8)	107 (79.3)	168 (75.7)	0.093
Bayley-III-NL Bayley motor score 70–84	94 (21.5)	23 (28.8)	25 (18.5)	46 (20.7)	
Bayley-III-NL Bayley motor score <70	17 (3.9)	6 (7.5)	3 (2.2)	8 (3.6)	
Vision, N (%) evaluated	533 (96.2)	95 (96.9)	170 (95.5)	268 (96.4)	
Normal	450 (84.4)	79 (83.2)	140 (82.4)	231 (86.1)	0.175
Mild visual problems including squints or refractive errors	67 (12.6)	16 (16.8)	23 (13.5)	28 (10.4)	
Functionally impaired vision or blindness	16 (3.0)	0 (0.0)	7 (4.1)	9 (3.4)	
Hearing, N (%) evaluated	529 (95.5)	94 (95.9)	171 (96.1)	264 (95.0)	
Normal	508 (96.0)	92 (97.9)	162 (94.7)	254 (96.2)	0.356
Mild hearing loss, not sufficient to require aids	16 (3.0)	2 (2.1)	8 (4.5)	6 (2.3)	
Hearing loss requiring aids or severe sensorineural hearing loss despite aids	5 (0.9)	0 (0.0)	1 (0.6)	4 (1.5)	
Neurological exam, N (%) evaluated	530 (95.7)	95 (96.9)	170 (95.5)	265 (95.3)	
Normal	440 (83.0)	72 (75.8)	142 (83.5)	226 (85.3)	0.116
Mildly abnormal (eg, posture, coordination or tone dysregulation disorders)	67 (12.6)	17 (17.9)	24 (14.1)	26 (9.8)	
CP	23 (4.3)	6 (6.3)	4 (2.4)	13 (4.9)	
Classification of CP					
Spastic unilateral	8 (34.8)	2 (33.3)	0 (0.0)	6 (46.2)	
Spastic bilateral	8 (34.8)	2 (33.3)	1 (25.0)	5 (38.5)	
Atactic	2 (8.7)	2 (33.)	0 (0.0)	0 (0.0)	
Dyskinetic	1 (4.3)	0 (0.0)	0 (0.0)	1 (7.7)	
Unclassifiable	4 (17.4)	0 (0.0)	3 (75.0)	1 (7.7)	
Classification according to GMFCS					
GMFCS I	7 (30.4)	3 (50.0)	0 (0.0)	4 (30.8)	
GMFCS II	5 (21.7)	1 (16.7)	1 (25.0)	3 (23.1)	
GMFCS III	3 (13.0)	1 (16.7)	0 (0.0)	2 (15.4)	
GMFCS IV	2 (8.7)	0 (0.0)	0 (0.0)	2 (15.4)	
Unknown	6 (26.1)	1 (16.7)	3 (75.0)	2 (15.4)	
CBCL Total T-score, N (%) evaluated	397 (71.7)	70 (71.4)	130 (73.0)	197 (70.9)	
CBCL Total T-score mean (SD)	48 (10)	49 (9)	47 (10)	48 (10)	0.717
CBCL Total T-score median (IQR)	47 (40–55)	47 (43–54)	47 (39–55)	48 (40–56)	0.677
CBCL Total T-score 60 or lower	358 (90.2)	64 (91.4)	118 (90.8)	176 (89.3)	0.605
CBCL Total T-score 61–70	34 (8.6)	4 (5.7)	11 (8.5)	19 (9.6)	
CBCL Total T-score >70	5 (1.3)	2 (2.9)	1 (0.8)	2 (1.0)	
CBCL Internalising T-score, N (%) evaluated	398 (71.8)	71 (72.4)	130 (73.0)	197 (70.9)	

Continued

Table 2 Continued

	Total	24 weeks	25 weeks	26 weeks	P value
CBCL internalising T-score mean (SD)	47 (11)	48 (9)	46 (11)	47 (11)	0.763
CBCL internalising T-score median (IQR)	45 (41–55)	47 (41–55)	45 (37–55)	45 (37–55)	0.712
CBCL internalising T-score 60 or lower	359 (90.2)	66 (93.0)	118 (90.8)	175 (88.8)	0.755
CBCL internalising T-score 61–70	33 (8.3)	5 (7.0)	10 (7.7)	18 (9.1)	
CBCL internalising T-score >70	6 (1.5)	0 (0.0)	2 (1.5)	4 (2.0)	
CBCL Externalising T-score, N (%) evaluated	398 (71.8)	71 (72.4)	130 (78.0)	197 (70.9)	
CBCL Externalising T-score mean (SD)	49 (10)	50 (9)	49 (10)	49 (10)	0.925
CBCL Externalising T-score median (IQR)	50 (42–56)	48 (44–56)	48 (42–56)	50 (42–56)	0.869
CBCL Externalising T-score 60 or lower	356 (89.4)	66 (93.0)	114 (87.7)	176 (89.3)	0.828
CBCL Externalising T-score 61–70	36 (9.0)	4 (5.6)	14 (10.8)	18 (9.1)	
CBCL Externalising T-score >70	6 (1.5)	1 (1.4)	2 (1.5)	3 (1.5)	
Impairment, including Bayley-III-NL cognitive score, vision, hearing and neurological exam, N (%) evaluated	554 (100)	98 (100)	178 (100)	278 (100)	
None	61.9% (58–66)	55.1% (45–65)	56.7% (49–64)	67.6% (62–73)	0.072
Mild	29.1% (25–33)	35.7% (27–46)	33.7% (27–41)	23.8% (19–29)	
Moderate-to-severe	9.0% (7–12)	9.2% (5–17)	9.6% (6–15)	8.6% (6–13)	
Impairment, including the above and also Bayley-III-NL motor score, N (%) evaluated	464 (83.8)	83 (84.7)	146 (82.0)	235 (84.5)	
None	53.0% (48–58)	43.4% (33–54)	51.4% (43–59)	57.4% (51–64)	0.225
Mild	34.3% (30–39)	43.4% (33–54)	35.6% (28–44)	30.2% (25–36)	
Moderate-to-severe	12.7% (10–16)	13.2% (8–22)	13.0% (8–19)	12.3% (9–17)	
Impairment, including the above and also CBCL T-scores, N (%) evaluated	364 (65.7)	69 (70.4)	118 (66.3)	177 (63.7)	
None	45.6% (41–51)	40.6% (30–52)	40.7% (32–50)	50.9% (44–58)	0.249
Mild	35.7% (31–41)	42.0% (31–54)	40.7% (32–50)	29.9% (24–37)	
Moderate-to-severe	18.7% (15–23)	17.4% (10–28)	18.6% (13–27)	19.2% (14–26)	

*Pairwise analysis showed a significant difference in Bayley-III-NL motor score between 24 weeks' and 25 weeks' gestation (p=0.014).

findings are that at 2 years' CA, 62% of survivors did not have impairment, whereas mild impairment was seen in 29%, and moderate-to-severe impairment (ie, NDI) in 9%. The percentage of surviving children with NDI was comparable between 24 weeks', 25 weeks' and 26 weeks' gestation. After multivariable analysis, severe brain injury and low maternal education were associated with higher odds on NDI. NDI-free survival was 48%, 67% and 75% in NICU-admitted infants at 24 weeks', 25 weeks' and 26 weeks' gestation, respectively.

Comparing our findings with other large national cohort studies from Europe shows lower rates of NDI in the EPI-DAF Study.[19 21 22] However, direct comparison with other studies

Table 3 Logistic regression to evaluate the effect of different perinatal factors on NDI

	NDI
	OR (95% CI)
GA (days)	0.98 (0.93 to 1.03)
Female	0.95 (0.53 to 1.79)
SGA	1.47 (0.66 to 3.07)
NEC	1.32 (0.51 to 3.02)
Severe brain injury	2.63 (1.32 to 5.05)*
Low maternal education	2.58 (1.26 to 5.03)*

Numbers are presented as OR with 95% CI. Being female was compared with the reference category of being male, low maternal education was compared with a reference category of intermediate–high education. *significant at 0.05 level.
GA, gestational age; NDI, neurodevelopmental impairment; NEC, necrotising enterocolitis ; SGA, small for gestational age.
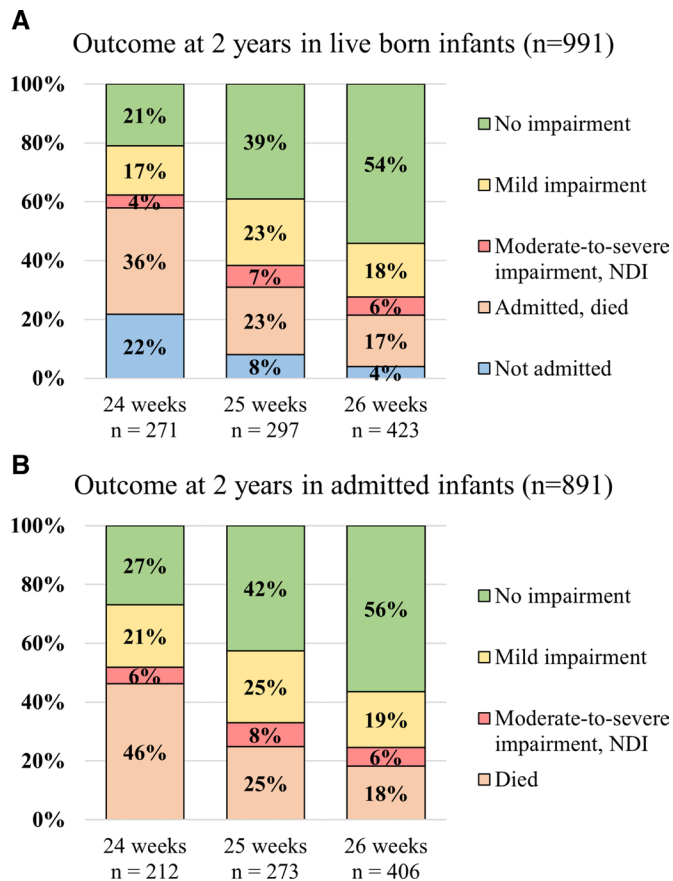
remains challenging, due to various sources of variation.[4] This variation is related, for example, to age at assessment, year of birth, socioeconomic conditions and differences in the management of extremely preterm children. One very important issue that precludes direct comparisons within and between countries is the lack of a consensus definition of NDI, which vary widely across studies.[23] The current study showed that adding motor function and behavioural data to the outcome definition resulted in a 25% decrease in children without any impairment at the cost of duplication of survivors with NDI. Note, however, that the percentage of NICU survivors with NDI was comparable between 24 weeks', 25 weeks' and 26 weeks' gestation, independent of the number of domains used for outcome classification. Compared with NDI, there is much less evidence regarding early behavioural, social and emotional outcomes.[20] However, behavioural impairments may have great impact on attention problems and socioemotional competence in (pre-) school years. For future research, there is a need for more standardised reporting of neurodevelopmental outcomes in very preterm children, which may include a stepwise approach as presented in our study.[4]

The current Dutch approach towards treatment initiation for extremely preterm infants is more conservative than in other countries.[24 25] Also, there is a more restrictive approach towards the continuation of life-sustaining treatment for extremely preterm infants, if there are concerns on potential serious disabilities and the infant's future quality of life.[25] Both approaches may result in differences in impairment rates. The period spanning from $24^{0/7}$ weeks' to $25^{6/7}$ weeks' gestation is considered in

Figure 1 (A) Imputed overall neurodevelopmental outcome, classified as no, mild or moderate-to-severe impairment (ie, NDI), using defined categories of cognitive development, neurological examination and neurosensory function for different GA groups, using all live-born infants as the denominator. (B) Imputed overall neurodevelopmental outcome, classified as no, mild or moderate-to-severe impairment (ie, NDI), using defined categories of cognitive development, neurological examination and neurosensory function, using all NICU-admitted infants as the denominator. GA, gestational age; NDI, neurodevelopmental impairment; NICU, neonatal intensive care unit. Figures might not add up to 100% due to rounding.

the Netherlands as a grey zone, in which management of infants born should be decided based on a consensus between the healthcare professionals and the parents, while other countries more often identify this grey zone as a period between 22 weeks and 24 weeks.[25 26] Differences between hospitals and countries in attitudes towards providing life support to the most immature infants seem to have the greatest impact on infants born in this grey zone and less on infants born at 26 weeks' gestation. Unfortunately, our registry does not provide any information on decisions during prenatal counselling and in the delivery room. These decisions might have influenced resuscitation and therefore might have influenced distribution of impairment among infants born at 24 weeks, 25 weeks and 26 weeks.

Although the group of children with moderate-to-severe impairment is clearly defined in the current study, the group of children with mild impairment is heterogeneous. Children with squints or mild refractive errors are similarly classified as children having an IQ-score between 70 and 85, while the latter might have greater impact on educational skills and future life. When classifying children with only mild hearing or vision problems as having no impairment, the rate of children without

any impairment would increase from 62% to 70%. Moreover, children with mild problems in multiple domains are classified as having mild impairment, while they may encounter much more limitations in their socioemotional competence and school career. Therefore, the group of mildly impaired children should be interpreted with caution, all the more because parents and healthcare professionals do not always agree on the perceived impact of impairment.[24]

In the Netherlands, two previous studies on follow-up of extremely preterm infants were performed prior to and just after the 2010 guideline change.[27 28] The first study reports on neurodevelopmental outcome at 2 years' CA of children born at 25 weeks' and 26 weeks' gestation in a period after lowering the threshold for active treatment from 26 weeks to 25 weeks, showing moderate-to-severe impairment in 17% and 9% of infants born at 25 weeks' and 26 weeks' GA, respectively. The second study reports on outcomes at 2 years' CA of children born at 24 weeks' and 25 weeks' gestation in a period directly after lowering the threshold for active treatment from 25 weeks to 24 weeks, reporting moderate-to-severe impairment in 20% and 12% for infants born at 24 weeks' and 25 weeks' GA, respectively. These data indicate that lowering the threshold for active treatment over time did not result in increased rates of survivors with NDI.

The current study presents data on neurodevelopmental outcome after preterm birth that can be used for prenatal counselling of parents. However, it is of great importance to adjust the counselling by taking into consideration the parental values and ideas about quality of life.[29 30] As such, the National Institute of Child Health in the UK advises to 'individualise the information to be provided, based on family preferences, wants and needs'.[31] Further exploration is needed on parental views of personalising prenatal counselling and on exactly what aspects of prenatal counselling should be personalised.[29]

The strengths of this study include the high follow-up rate (85%), the national approach and the extensive data collection over a period of 3 years in a contemporaneous cohort. Follow-up was performed in a standardised way during regular outpatient clinic visits using a nationwide guideline.[12] As children lost to follow-up are more often born to parents of lower SES, a multiple imputation model including an SES variable that was available from the registry was used to account for possible selective missing data. However, this study has some limitations as well. We did not have access to a term comparison group. Some other studies adjust the threshold of the composite Bayley scores for the substantially higher mean scores that are often observed in the general population compared with the test norm mean of 100. However, the Bayley-III-NL norms are recently developed and based on a representative population, making it very likely that the current norm of 100 (SD 15) is a realistic assumption.[16] Second, assessment of the language scale of the Bayley-III-NL is not part of the standardised follow-up programme for extremely preterm infants in the Netherlands. Therefore, language development could not be included in the current study. Furthermore, GA was not blinded for examiners, which might have introduced information bias. Visual and hearing problems were identified using parental information on medical history of the child, which might have resulted in a less precise definition. The national neonatal registry did not contain reliable information on several morbidities, such as antenatal corticosteroids and bronchopulmonary dysplasia. Lastly, neurodevelopmental outcomes at 2 years' CA may significantly underestimate the risk of significant NDI later in childhood.[32]

CONCLUSIONS

Within a decade after lowering the threshold for supporting active treatment from 25 completed weeks' to 24 completed weeks' gestation, a majority of the surviving preterm infants born before 27 weeks' gestation did not have any impairment at 2 years' CA. The change in intervention threshold and subsequent improvement in survival at 24 weeks have not been accompanied by a large increase in survivors with NDI. The percentage of survivors with NDI was comparable for infants born at 24 weeks', 25 weeks' and 26 weeks' gestation. Among all live-born and NICU-admitted infants, an increase in NDI-free survival was observed from 24 weeks' to 26 weeks' gestation. This description of a national cohort with high follow-up rates gives an accurate description of the range of outcomes that may occur after extremely preterm birth.

Author affiliations
[1]Department of Neonatology, Máxima Medical Center, Veldhoven, Noord-Brabant, The Netherlands
[2]Department of Neonatology, Willem-Alexander Children's Hospital, Leiden University Medical Center, Leiden, The Netherlands
[3]The Netherlands Perinatal Registry, Utrecht, The Netherlands
[4]Department of Neonatology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[5]Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands
[6]Department of Neonatology, VU University Medical Center, Amsterdam University Medical Center, Amsterdam, The Netherlands
[7]Department of Neonatology, Isala Clinics, Zwolle, The Netherlands
[8]Department of Perinatology, Amalia Children's Hospital, Radboud University Medical Center, Nijmegen, The Netherlands
[9]Department of Neonatology, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands
[10]Department of Neonatology, Maastricht University Medical Centre, Maastricht, The Netherlands
[11]Department of Obstetrics and Gynaecology, Máxima Medical Center, Veldhoven, The Netherlands
[12]Department of Electrical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands
[13]Department of Neonatology, Emma Children's Hospital, Amsterdam University Medical Centre, Amsterdam, The Netherlands
[14]Department of Neonatology, Máxima Medical Center, Veldhoven, The Netherlands
[15]Department of Applied Physics, School of Medical Physics and Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands

ORCID iDs
Pauline E van Beek http://orcid.org/0000-0001-8553-3241
Peter Andriessen http://orcid.org/0000-0002-5159-6874

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