Perinatal risk indicators for long-term neurological morbidity among preterm neonates

OBSTETRICS

Perinatal risk indicators for long-term neurological morbidity among preterm neonates

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OBJECTIVE: Many obstetric interventions are performed to improve long-term neonatal outcome. However, long-term neonatal outcome is usually not a primary outcome because it is time-consuming and expensive. The aim of this project was to identify different perinatal risk indicators and to develop prediction models for neurologic morbidity at 2 and 5 years of age.

STUDY DESIGN: Data from a Dutch cohort study of preterm and small-for-gestational-age infants was used. Neonates who were born in The Netherlands in 1983 with a gestational age of <34 weeks and without congenital abnormalities were included (n = 753). Infants were divided in 3 groups: no handicap, minor handicap, and major handicap.

RESULTS: Common risk indicators for major handicaps at 2 and 5 years of age were male sex (odds ratio, 2.7 and 3.0, respectively), seizures after ≥2 days of life (odds ratio, 5.8 and 5.8, respectively), and intracranial hemorrhage (odds ratio, 3.8 and 2.6, respectively).

CONCLUSION: In this cohort, male sex, intracranial hemorrhage, and seizures seem to be important risk indicators for long-term neurologic morbidity.

Key words: long-term neurologic morbidity, perinatal risk indicator, prediction model, premature

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Many obstetric interventions are performed to improve both short- and long-term outcome. Evaluation of the long-term effect of a perinatal intervention is necessary because serious sequelae from perinatal complications frequently manifest themselves only after several years. Nevertheless, long-term follow-up evaluation is time-consuming, expensive, beyond obstetricians' awareness, and falls outside the funding period of most obstetric studies. Consequently, obstetric interventions usually are not evaluated for their long-term outcomes, and short-term outcomes are selected as the primary endpoint of an obstetric study.

One way to overcome this problem would be to model long-term consequences on the basis of short-term neonatal outcomes. This could be realized by the development of prediction models in which the association between short-term and long-term outcomes is determined statistically and adjusted for relevant covariates.

Subsequently, these prediction models for long-term neurologic morbidity could be used to extrapolate short-term outcomes on the neurologic status of neonates or to indicate for which neonates neurologic long-term follow-up evaluation is required, as their outcomes (either absence or presence of sequelae) cannot be predicted from short-term outcomes and clinical background characteristics. The development of such models requires a longitudinal approach in which data surrounding pregnancy, delivery, and short-term outcomes and follow-up data are available on various health-related outcomes.

The Dutch project on preterm and small-for-gestational-age infants (POPS) cohort is one of the few birth cohorts with a systematic assessment of these data. Data of all Dutch infants who were born alive in 1983 with a gestational age of <32 completed weeks and/or with a birthweight of <1500 g were collected prospectively.[1-5] This birth cohort could provide insight in the long-term consequences of perinatal outcomes.

In the literature, many risk indicators for neurologic morbidity are mentioned. Birth catastrophes such as placental abruption, cord prolapse, and uterine rup-

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ture sharply increase the risk for neurologic morbidity, but these conditions fortunately are uncommon and even sometimes not survived; individually and collectively, these indicators account for only a small portion of neurologic morbidity. Although any other indicator, if severe, may be sufficient to cause neurologic morbidity, more often it is the presence of multiple risk indicators that causes neurologic morbidity later in life.[6] Development of multivariable prediction models for neurologic morbidity can increase our understanding of predictors for neurologic morbidity and can help us to develop interventions to prevent these complications in the future.

In this study, we aimed to identify different perinatal risk indicators for long-term neurologic morbidity and to use these perinatal risk indicators to develop prediction models for long-term neurologic morbidity at 2 and 5 years of age.

MATERIALS AND METHODS

Study design

For the development of prediction models for long-term neurologic morbidity, we used data that were available from a Dutch cohort study of preterm and/or small-for-gestational-age infants (POPS study). In this cohort, all of the live born infants who were included were delivered in The Netherlands between January and December 1983, either at <32 completed weeks of gestation and/or with a birthweight of <1500 g. The study ultimately consisted of 1338 infants, which was 94% of the eligible infants who had been born in 1983 in The Netherlands.[1-5] Because of the "mixed metaphor" of combining gestational age and low birthweight in this cohort, only infants with gestational age of <34 weeks were included in our analysis. Infants with congenital abnormalities were excluded.

Outcomes

Endpoints that were used for this prediction model were neurologic morbidity at 2 and 5 years of age. The follow-up evaluation until the age of 2 years was carried out by local pediatricians all over The Netherlands. An overall developmental level was done with the Gesell test that had been adapted for Dutch children and also neurologic, visual, and hearing examinations had been performed.

According to the outcome, the data were divided into 3 groups: no handicap, minor handicap, and major handicap. The infant was considered to have no handicap when developmental delay was absent (developmental quotient >90) and there were no motor, visual, or hearing disabilities. A minor handicap was diagnosed when some delay was present (3-4 months retarded or developmental quotient between 80 and 90) and/or at least one of the following handicaps: a mild cerebral paresis (such a slight hemiparesis or quadriparesis), mild visual or hearing defects, or moderate psychosocial problems. Such disabilities were unlikely to prevent the child from going to a normal school or to interfere seriously with normal life. A major handicap was diagnosed when severe retardation was present (≥5 months delay or developmental quotient <80) and/or at least one of the following handicaps: a severe cerebral paresis, severe visual or hearing defects, or serious psychologic problems. Such disabilities probably would stop the child from going to a normal school or cause serious interference with normal functioning in society.

At 5 years chronologic age, a follow-up program was carried out by 3 specially trained pediatricians during a visit to the home. Eight areas of development were assessed: neuromotor function (Touwen[7]); mental development (Denver developmental screening test)[8]; hearing function (audiometry/otoscopy); visual function; language and speech development (Standardized Dutch Test; Gerritsen[9]); musculoskeletal system (physical examination) and respiratory morbidity (parents' questionnaire). In each area, an infant was categorized as impaired, disabled, or handicapped, according to World Health Organization definitions.[10] An infant was regarded as handicapped at 5 years of age if he or she had a handicap in an area of examination. Infants who needed special education as a result of ≥1 impairments or disabilities were considered to be at least minor handicapped. A handicap was considered minor if it did not interfere seriously with everyday life and did not require extensive caretaking and major when it did interfere with everyday life and when it led to a life of dependency or institutionalization.[5,10]

Candidate predictors

Candidate predictors for neurodevelopment handicaps were determined on the basis of existing literature of perinatal predictors for long-term neurologic morbidity, combined with consulting experts in the field.[6,11-15] The following candidate predictors were included in the analysis: social class, ethnicity, education level of the mother (low, moderate, high), maternal smoking, hypertension before pregnancy, pregnancy-induced hypertension (diastolic pressure >90 mm Hg), preeclampsia/eclampsia, maternal epilepsy, diabetes mellitus, gestational diabetes mellitus, multiple pregnancy, vertex or other presentation, prolonged rupture of membranes, meconium-stained fluid, glucocorticosteroids, small for gestational age (<10th percentile), gestational age, sex, neonatal asphyxia, respiratory distress syndrome, bronchopulmonary dysplasia, seizures, intracranial hemorrhage, necrotizing enterocolitis, hyperbilirubinemia, sepsis (blood culture proven), and duration of mechanical ventilation (continuous or intermittent).

Neonatal asphyxia was defined as low 5-minute Apgar score (<7) and/or umbilical cord acidosis (pH <7.05). *Bronchopulmonary dysplasia* was defined as clinical signs of respiratory distress, with an abnormal chest X-ray and an oxygen requirement after 28 days of age (criteria of Bancalari et al[16]). *Intracranial hemorrhage* was defined as a clinical diagnosis (based on rapid or salutatory deterioration, fall in hematocrit level) and/or ultrasound scans or computed tomography. All seizures (clinical definition: including subtle seizures, generalized tonic, multifocal clonic, focal clonic, and myoclonic seizures) were recorded as either absent or as present on day 1 of life or day 2 of life or later.

Statistical analysis

We developed 4 multivariable logistic regression models in which we analyzed the association between the candidate predictors and infants with minor or major handicap vs infants with no hand-

icap and infants with major handicap vs infants with no or minor handicap at 2 and 5 years of age. Multiple imputations were used to adjust for missing values. We created 5 imputed datasets that were based on the candidate predictors mentioned earlier and all available outcome-specific data at 2 and 5 years of age. Imputed values were limited to the lowest and highest values that were observed for the measured outcome variable. Uncertainty about imputed values is reflected in differences between different imputed datasets and incorporated in the estimated standard errors and associated probability values for the pooled model. We used SPSS software (version 17.0; SPSS Inc, Chicago, IL) for the imputation. The imputation method in SPSS software is based largely on the chained equations approach in multivariate imputation by chained equations (MICE).[17]

After imputation, the prevalence of the candidate predictors was first analyzed. Thereafter, a univariable and multivariable regression analysis was performed to estimate odds ratios (ORs), 95% confidence interval [CI], and corresponding probability values for dichotomous and continuous variables. Because the use of too stringent probability values for variable selection is more deleterious for a model than including too many factors, all variables that showed a significance level of $< .50$ in univariable analyses were entered in the multivariable logistic regression model.[18] Furthermore, we used a stepwise backward selection procedure with a predefined significance level of $< .20$ for removing variables from the models.[19] Variables that remained in the last step of the backward selection procedure in at least 4 of the 5 imputed datasets were included in the final logistic regression analysis. Discriminative capacity of the models was evaluated by calculation of the area under the curve. Calibration of the models was assessed by comparison of the calculated probabilities with the observed proportion of neurologic morbidity. The goodness-of-fit was tested formally with the Hosmer and Lemeshow test statistic. Data were analyzed with the SPSS software.

RESULTS

Sample and respiratory morbidity incidence

Of the original cohort of 1338 infants, 1026 infants survived the neonatal period (>28 days); 969 infants were alive at 2 years of age; 966 infants were alive at 5 years of age, and 959 infants were alive at 19 years of age. The risk of death in the first 28 days of life was equal for boys and girls. Because of the "mixed metaphor" of the combination of gestational age and low birthweight in this cohort, infants with a gestational age of ≥34 weeks were excluded (n = 136). Because congenital malformations were considered to influence neurologic function, all infants with congenital abnormalities were also excluded (n = 70), which left 753 infants for the final analysis. At 2 years of age, information on neurologic morbidity was missing for 23 infants (follow-up rate, 97%). At 5 years of age, information on neurologic morbidity was missing for 33 infants (follow-up rate, 96%). At 2 years of age, the rate of infants with no handicap, minor handicap, or major handicap was 83.2% (n = 607 infants), 11.5% (n = 84 infants), and 5.3% (n = 39 infants), respectively, before imputation and 81.5% (n = 614 infants), 11.7% (n = 88 infants), and 6.8% (n = 51 infants), respectively, after imputation. At 5 years of age, the rate of infants with no handicap, a minor handicap, or a major handicap was 86.0% (n = 619 infants), 8.3% (n = 60 infants), and 5.7% (n = 41 infants), respectively, before imputation and 84.5% (n = 636 infants), 9.4% (n = 71 infants), and 6.1% (n = 46 infants), respectively, after imputation.

Univariable and multivariable models

Neurologic morbidity at 2 years of age. Tables 1 and 2 show the results of the univariable and multivariable regression analysis for neurologic morbidity at 2 years of age. Male sex (adjusted OR [aOR], 1.6; 95% CI, 1.1–2.4) and intracranial hemorrhage that was diagnosed with ultrasound scanning or computed tomography (aOR, 2.3; 95% CI, 1.2–4.3) were significant risk indicators for minor/major handicaps at 2 years of age (Table 1). Risk indicators for major handicaps only were male sex (aOR, 2.7; 95% CI, 1.2–5.8), seizures at ≥2 days of life (aOR, 5.8; 95% CI, 1.9–17.8), intracranial hemorrhage that was diagnosed with ultrasound scanning or computed tomography (aOR, 3.8; 95% CI, 1.6–9.1) and hyperbilirubinemia (aOR, 2.6; 95% CI, 1.2–5.3). Surprisingly, maternal smoking (1-10 cig/d) seemed to decrease the risk for major handicaps (aOR, 0.32; 95% CI, 0.12–0.88) (Table 2).

Neurologic morbidity at 5 years of age. Tables 3 and 4 show the results of the univariable and multivariable regression analysis for neurologic morbidity at 5 years of age. Multiple pregnancy (aOR, 1.8; 95% CI, 1.1–3.1), low birthweight (aOR, 1.8; 95% CI, 1.1–3.0), male sex (aOR, 2.2; 95% CI, 1.4–3.6), bronchopulmonary dysplasia (aOR, 2.0; 95% CI, 1.1–3.8), and intracranial hemorrhage that was diagnosed with ultrasound scanning or computed tomography (aOR, 2.5; 95% CI, 1.2–5.4) were significant risk indicators for minor/major handicaps (Table 3). Higher social class decreased the risk for neurologic morbidity (aOR, 0.40; 95% CI, 0.19–0.87). Risk indicators for major handicaps only were male sex (aOR, 3.0; 95% CI, 1.1–8.0), seizures at ≥2 days of life (aOR, 5.8; 95% CI, 1.9–17.9), and intracranial hemorrhage that was diagnosed with ultrasound scanning or computed tomography (aOR, 2.6; 95% CI, 1.02–6.8) (Table 4).

Model performance. The 4 prediction models (that compared infants with minor or major handicap vs infants without a handicap and infants with a major handicap vs infants with no handicap or minor handicap) discriminated modestly well between diseased and nondiseased infants with an area under the curve of 0.67 (95% CI, 0.62–0.72) and 0.76 (95% CI, 0.69–0.83) at 2 years of age, respectively, and an area under the curve of 0.74 (95% CI, 0.69–0.79) and 0.74 (95% CI, 0.67–0.81) at 5 years of age, respectively. Overall, the 4 prediction models showed good calibration (Figures 1 and 2). Nevertheless, the calibration for neurologic morbidity at 2 years of age seems better than the calibration for neurologic morbidity at 5 years of age, but this is understandable

TABLE 1
Risk indicators for neurological morbidity (2 years); infants with minor/major handicap vs infants with no handicap

Candidate predictors	No. of children (pooled)	Univariable analysis (pooled) Crude odds ratio (95% CI)	*P* value	Multivariable analysis (pooled) Adjusted odds ratio (95% CI)	*P* value
Environmental factors					
Ethnicity					
Both parents white	637 (85%)	1.2 (0.68–2.2)	.489		
One/both parents Mediterranean	41 (5%)	1.1 (0.41–3.0)	.824		
One/both parents black	31 (4%)	0.54 (0.16–1.8)	.322		
One/both parents Asian	39 (5%)	0.66 (0.24–1.8)	.421		
Other	9 (1%)				
Social class					
Low	295 (39%)	1.0			
Moderate	275 (37%)	0.76 (0.46–1.2)	.274		
High	183 (24%)	0.71 (0.40–1.3)	.256		
Education mother					
Low	423 (56%)	0.84 (0.48–1.5)	.531		
Moderate	131 (17%)	0.88 (0.54–1.4)	.606		
High	199 (26%)				
Maternal smoking during pregnancy per day					
No	493 (65%)	1.0			
1-10	147 (20%)	1.05 (0.64–1.7)	.860		
≥10	112 (15%)	1.4 (0.82–2.4)	.220		
Hypertension before pregnancy	34 (5%)	0.74 (0.28–2.0)	.548		
Epilepsy	4 (1%)	1.8 (0.15–20.7)	.645		
Obstetric					
Multiple pregnancy	172 (23%)	1.0 (0.64–1.6)	.995		
Corticosteroids	131 (17%)	1.2 (0.72–1.9)	.543		
Gestational diabetes mellitus					
No	715 (95%)	1.0			
With diet	22 (3%)	0.43 (0.1–1.9)	.258		
With insulin	16 (2%)	0.97 (0.27–3.5)	.964		
Hypertension during pregnancy					
No	583 (77%)	1.0			
≥90 mm Hg	110 (15%)	0.73 (0.41–1.3)	.281		
Preeclampsia/eclampsia	60 (8%)	0.68 (0.32–1.5)			
Prolonged rupture of membranes					
No	440 (58%)	1.0			
<1-11 h	127 (17%)	1.2 (0.69–1.9)	.611		
12-24 h	28 (4%)	1.4 (0.50–3.8)	.544		
1-7 D	106 (14%)	1.05 (0.60–1.9)	.855		
>7 D	53 (7%)	1.5 (0.74–2.9)	.271		

Teune. Perinatal risk indicators for long-term neurological morbidity. Am J Obstet Gynecol 2011. *(continued)*

TABLE 1
Risk indicators for neurological morbidity (2 years); infants with minor/major handicap vs infants with no handicap *(continued)*

Candidate predictors	No. of children (pooled)	Univariable analysis (pooled) Crude odds ratio (95% CI)	*P* value	Multivariable analysis (pooled) Adjusted odds ratio (95% CI)	*P* value
Meconium stained fluid	41 (5%)	1.3 (0.57–3.0)	.524		
Presentation: other than vertex	231 (31%)	0.88 (0.58–1.3)	.550		
Neonatal					
Gestational age, wk		0.93 (0.83–1.03)	.168		
25-28	108 (14%)				
28-30	219 (29%)				
30-32	320 (43%)				
32-34	106 (14%)				
Low birthweight (<10th percentile)	197 (26%)	0.95 (0.62–1.5)	.829		
Male sex	396 (53%)	1.7 (1.2–2.5)	.006	1.6 (1.1–2.4)	.014
Asphyxia	71 (9%)	2.3 (1.2–4.3)	.016	1.8 (0.92–3.6)	.094
Bronchopulmonary dysplasia	112 (15%)	1.9 (1.1–3.2)	.020		
Respiratory distress syndrome					
No	421 (56%)	1.0			
Clinical	111 (15%)	1.02 (0.58–1.8)	.935		
Radiographic	221 (29%)	1.3 (0.87–2.0)	.192		
Pneumothorax	50 (7%)	1.1 (0.53–2.4)	.736		
Seizures					
No	724 (96%)	1.0		1.0	
First d	4 (1%)	2.3 (0.19–27.5)	.520	2.6 (0.20–34.4)	.469
≥2 d	26 (3%)	2.8 (1.2–6.4)	.018	2.1 (0.83–5.3)	.120
Intracranial hemorrhages					
No	653 (87%)	1.0		1.0	
Suspect	41 (5%)	1.5 (0.71–3.3)	.279	0.94 (0.41–2.1)	.874
Proven	58 (8%)	2.9 (1.6–5.3)	.000	2.3 (1.2–4.3)	.009
Necrotizing enterocolitis	42 (6%)	2.1 (1.02–4.4)	.046	2.1 (0.95–4.5)	.069
Hyperbilirubinemia ≥200 μmol/L	212 (28%)	1.5 (1.01–2.4)	.047	1.5 (0.97–2.4)	.071
Sepsis (culture proven)	78 (10%)	1.5 (0.83–2.6)	.192	1.5 (0.80–2.7)	.221
Continuous positive airway pressure, d	mean = 2 days	1.03 (0.99–1.1)	.114		
Artificial ventilation, d	mean = 3 days	1.04 (1.01–1.1)	.004	1.02 (0.99–1.05)	.125

CI, confidence interval.

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because it is harder to predict an outcome later in life. The Hosmer-Lemeshow goodness-of-fit test was not significant for all 4 prediction models.

Comment

We developed 4 prediction models for neurologic morbidity at 2 and 5 years of age for infants who were delivered in The Netherlands (1983) at <34 weeks of gestation. We developed models to predict which infants would develop any handicap compared with completely healthy infants, and we developed models to predict which infants would experience a major handicap compared with infants who experienced no handicap or, at maximum, a minor handicap.

The 4 prediction models discriminated modestly well between infants with and without handicaps and showed good calibration. The relative importance of discrimination and calibration depends on the clinical applications of a

TABLE 2
Risk indicators for neurological morbidity (2 years); infants with a major handicap vs infants with no or minor handicap

Candidate predictors	No. of children (pooled)	Univariable analysis (pooled) Crude odds ratio (95% CI)	*P* value	Multivariable analysis (pooled) Adjusted odds ratio (95% CI)	*P* value
Environmental factors					
Ethnicity					
Both parents white	637 (85%)	1.2 (0.43–3.3)	.724		
One/both parents Mediterranean	41 (5%)	1.4 (0.28–6.8)	.691		
One/both parents black	31 (4%)	0.62 (0.07–5.1)	.654		
One/both parents Asian	39 (5%)		.998		
Other	9 (1%)				
Social class					
Low	295 (39%)	1.0			
Moderate	275 (37%)	0.73 (0.35–1.5)	.407		
High	183 (24%)	0.68 (0.25–1.8)	.458		
Education mother					
Low	423 (56%)	1.0			
Moderate	131 (17%)	1.4 (0.60–3.4)	.436		
High	199 (26%)	1.1 (0.45–2.9)	.784		
Maternal smoking during pregnancy per day					
No	493 (65%)	1.0		1.0	
1-10	147 (20%)	0.45 (0.18–1.2)	.100	0.32 (0.12–0.88)	.028
≥10	112 (15%)	0.62 (0.20–2.0)	.429	0.61 (0.14–2.5)	.501
Hypertension before pregnancy	34 (5%)		1.000		
Epilepsy	4 (1%)		1.000		
Obstetric					
Multiple pregnancy	172 (23%)	1.5 (0.78–2.9)	.218		
Corticosteroids	131 (17%)	1.5 (0.69–3.1)	.331		
Gestational diabetes mellitus					
No	715 (95%)	1.0			
With diet	22 (3%)	0.63 (0.08–4.8)	.656		
With insulin	16 (2%)		1.000		
Hypertension during pregnancy					
No	583 (77%)	1.0			
≥90 mm Hg	110 (15%)	0.65 (0.24–1.8)	.391		
Preeclampsia/eclampsia	60 (8%)	0.56 (0.14–2.3)	.417		
Prolonged rupture of membranes					
No	440 (58%)	1.0			
<1-11 h	127 (17%)	1.7 (0.78–3.5)	.191		
12-24 h	28 (4%)		.999		
1-7 d	106 (14%)	1.2 (0.46–3.1)	.716		
>7 d	53 (7%)	0.76 (0.19–3.1)	.708		

Teune. Perinatal risk indicators for long-term neurological morbidity. Am J Obstet Gynecol 2011. *(continued)*

TABLE 2
Risk indicators for neurological morbidity (2 years); infants with a major handicap vs infants with no or minor handicap *(continued)*

Candidate predictors	No. of children (pooled)	Univariable analysis (pooled) Crude odds ratio (95% CI)	*P* value	Multivariable analysis (pooled) Adjusted odds ratio (95% CI)	*P* value
Meconium stained fluid	41 (5%)	0.73 (0.12–4.3)	.728		
Presentation: other than vertex	231 (31%)	0.57 (0.27–1.2)	.140		
Neonatal					
Gestational age, wk		0.83 (0.70–0.98)	.030		
25-28	108 (14%)				
28-30	219 (29%)				
30-32	320 (43%)				
32-34	106 (14%)				
Low birthweight (<10th percentile)	197 (26%)	1.1 (0.54–2.2)	.796		
Male sex	396 (53%)	2.6 (1.3–5.3)	.009	2.7 (1.2–5.8)	.016
Asphyxia	71 (9%)	1.03 (0.37–2.9)	.958		
Bronchopulmonary dysplasia	112 (15%)	3.0 (1.03–9.0)	.074	2.1 (0.65–6.8)	.246
Respiratory distress syndrome					
No	421 (56%)	1.0			
Clinical	111 (15%)	1.3 (0.57–2.9)	.552		
Radiographic	221 (29%)	0.85 (0.41–1.7)	.648		
Pneumothorax	50 (7%)	0.80 (0.20–3.2)	.754		
Seizures					
No	724 (96%)	1.0		1.0	
First d	4 (1%)	6.4 (0.58–70.7)	.130	10.7 (0.67–172.0)	.096
≥2 d	26 (3%)	7.3 (2.9–18.5)	.000	5.8 (1.9–17.8)	.003
Intracranial hemorrhage					
No	653 (87%)	1.0		1.0	
Suspect	41 (5%)	1.6 (0.47–5.2)	.465	0.68 (0.16–2.9)	.602
Proven	58 (8%)	4.8 (2.1–10.8)	.000	3.8 (1.6–9.1)	.003
Necrotizing enterocolitis	42 (6%)	0.91 (0.15–5.4)	.916		
Hyperbilirubinemia ≥200 μmol/L	212 (28%)	2.2 (1.2–4.0)	.017	2.6 (1.2–5.3)	.014
Sepsis (culture proven)	78 (10%)	1.8 (0.81–4.0)	.153	2.0 (0.83–5.0)	.123
Continuous positive airway pressure, d	mean = 2 days	1.05 (1.00–1.1)	.069		
Artificial ventilation, d	mean = 3 days	1.04 (1.01–1.08)	.014		

CI, confidence interval.

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model. Because our models are intended to evaluate the neurologic long-term effects of perinatal interventions, the accuracy of the numeric probability (calibration) is relevant, less so than to identify adequately those infants with and without long-term neurologic morbidity.[20]

One major strength of this study is the relatively large national cohort with high follow-up rates that allows for a population-based prospective evaluation of the association between perinatal and demographic risk indicators on long-term neurologic morbidity. Handicaps were defined in a comprehensive way by taking general health, cerebral paresis, and hearing, vision, language, and mental development into account.

A relative limitation is that the infants in our cohort were born in 1983. Important progress in obstetrics and

TABLE 3
Risk indicators for neurological morbidity (5 years); infants with minor/major handicap vs infants with no handicap

Candidate predictors	No. of children (pooled)	Univariable analysis (pooled) Crude odds ratio (95% CI)	*P* value	Multivariable analysis (pooled) Adjusted odds ratio (95% CI)	*P* value
Environmental factors					
Ethnicity					
Both parents white	637 (85%)	1.6 (0.82–3.0)	.172		
One/both parents Mediterranean	41 (5%)	0.87 (0.30–2.5)	.793		
One/both parents black	31 (4%)	1.00 (0.34–3.0)	.996		
One/both parents Asian	39 (5%)	0.22 (0.02–1.9)	.176	0.19 (0.02–1.8)	.152
Other	9 (1%)				
Social class					
Low	295 (39%)	1.0		1.0	
Moderate	275 (37%)	0.68 (0.43–1.1)	.093	0.61 (0.35–1.1)	.091
High	183 (24%)	0.47 (0.26–0.84)	.012	0.40 (0.19–0.87)	.022
Education mother					
Low	423 (56%)	1.0		1.0	
Moderate	131 (17%)	1.3 (0.77–2.3)	.308	1.9 (0.94–3.7)	.077
High	199 (26%)	0.65 (0.33–1.3)	.219	1.1 (0.49–2.5)	.804
Maternal smoking during pregnancy per day					
No	493 (65%)	1.0			
1-10	147 (20%)	0.89 (0.50–1.6)	.685		
≥10	112 (15%)	1.1 (0.58–2.0)	.814		
Hypertension before pregnancy	34 (5%)	0.70 (0.24–2.1)	.519		
Epilepsy	4 (1%)		1.000		
Obstetric					
Multiple pregnancy	172 (23%)	1.8 (1.2–2.9)	.009	1.8 (1.1–3.1)	.022
Corticosteroids	131 (17%)	1.3 (0.81–2.2)	.251		
Gestational diabetes mellitus					
No	715 (95%)	1.0		1.0	
With diet	22 (3%)	2.0 (0.77–5.3)	.151	2.9 (0.98–8.4)	.055
With insulin	16 (2%)	0.36 (0.05–2.7)	.320	0.43 (0.05–3.4)	.422
Hypertension during pregnancy					
No	583 (77%)	1.0			
≥90 mm Hg	110 (15%)	0.71 (0.4–1.3)	.281		
Preeclampsia/eclampsia	60 (8%)	0.55 (0.23–1.3)	.180		
Prolonged rupture of membranes					
No	440 (58%)	1.0			
<1-11 h	127 (17%)	1.2 (0.65–2.1)	.607		
12-24 h	28 (4%)	1.2 (0.40–3.6)	.749		
1-7 d	106 (14%)	0.91 (0.45–1.8)	.785		
>7 d	53 (7%)	1.4 (0.67–3.0)	.371		

Teune. Perinatal risk indicators for long-term neurological morbidity. Am J Obstet Gynecol 2011. *(continued)*

TABLE 3
Risk indicators for neurological morbidity (5 years); infants with minor/major handicap vs infants with no handicap *(continued)*

Candidate predictors	No. of children (pooled)	Univariable analysis (pooled) Crude odds ratio (95% CI)	*P* value	Multivariable analysis (pooled) Adjusted odds ratio (95% CI)	*P* value
Meconium stained fluid	41 (5%)	1.2 (0.51–2.9)	.655		
Presentation: other than vertex	231 (31%)	1.1 (0.74–1.7)	.577		
Neonatal					
Gestational age, wk		0.45 (0.40–0.51)	.183		
25-28	108 (14%)				
28-30	219 (29%)				
30-32	320 (43%)				
32-34	106 (14%)				
Low birthweight (<10th percentile)	197 (26%)	1.4 (0.92–2.2)	.115	1.8 (1.1–3.0)	.015
Male sex	396 (53%)	2.7 (1.7–4.2)	.000	2.2 (1.4–3.6)	.001
Asphyxia	71 (9%)	1.9 (0.98–3.6)	.062	1.8 (0.86–3.6)	.124
Bronchopulmonary dysplasia	112 (15%)	2.7 (1.5–4.7)	.002	2.0 (1.1–3.8)	.034
Respiratory distress syndrome					
No	421 (56%)	1.0			
Clinical	111 (15%)	1.4 (0.76–2.5)	.295		
Radiographic	221 (29%)	1.6 (0.98–2.5)	.062		
Pneumothorax	50 (7%)	1.1 (0.51–2.5)	.756		
Seizures					
No	724 (96%)	1.0		1.0	
First d	4 (1%)	2.3 (0.21–24.3)	.498	3.1 (0.27–35.9)	.363
≥2 d	26 (3%)	3.5 (1.4–8.8)	.008	3.0 (1.1–8.6)	.036
Intracranial hemorrhage					
No	653 (87%)	1.0		1.0	
Suspect	41 (5%)	1.2 (0.48–3.0)	.706	0.96 (0.34–2.7)	.938
Proven	58 (8%)	2.9 (1.5–5.6)	.003	2.5 (1.2–5.4)	.015
Necrotizing enterocolitis	42 (6%)	0.87 (0.32–2.4)	.776		
Hyperbilirubinemia ≥200 μmol/L	212 (28%)	1.3 (0.76–2.0)	.384	1.3 (0.78–2.3)	.292
Sepsis (culture proven)	78 (10%)	1.4 (0.75–2.7)	.281		
Continuous positive airway pressure, d	mean = 2 days	1.03 (0.99–1.1)	.180		
Artificial ventilation, d	mean = 3 days	1.04 (1.01–1.07)	.012		

CI, confidence interval.

Teune. Perinatal risk indicators for long-term neurological morbidity. Am J Obstet Gynecol 2011.

neonatal care has improved the survival of increasingly premature infants, but the prevalence of moderate-to-severe disabilities (such as cerebral palsy) remains high. Like mortality rates, rates of disability generally increase with decreasing gestational age and birthweight.[21]

In a Canadian population-based study that was initiated in 2005, the prevalence of cerebral palsy at 2 years of age was 9.8% among 172 infants who were born at 22-28 weeks of gestation. The prevalence of cerebral palsy in the same regional area in 1991-1992 among 225 infants was 11%.[22] Rates of severe developmental delay and severe disability were lower in 2005 (3.7%/3.7%, respectively) than in the very preterm survivors who were born in 1991-1992 and 1997 (7.3%/7.8% and 14.8%/15.4%, respectively).

Furthermore, the prevalence of handicaps at 2 and 5 years of age is probably underestimated in the POPS cohort be-

TABLE 4
Risk indicators for neurological morbidity (5 years); infants with a major handicap vs infants with no or minor handicap

Candidate predictors	No. of children (pooled)	Univariable analysis (pooled) Crude odds ratio (95% CI)	*P* value	Multivariable analysis (pooled) Adjusted odds ratio (95% CI)	*P* value
Environmental factors					
Ethnicity					
Both parents white	637 (85%)	3.5 (0.60–20.7)	.172		
One/both parents Mediterranean	41 (5%)	0.54 (0.08–3.9)	.548		
One/both parents black	31 (4%)		.999		
One/both parents Asian	39 (5%)		.998		
Other	9 (1%)				
Social class					
Low	295 (39%)	1.0			
Moderate	275 (37%)	1.4 (0.64–3.0)	.410		
High	183 (24%)	0.78 (0.27–2.2)	.641		
Education mother					
Low	423 (56%)	1.0			
Moderate	131 (17%)	1.5 (0.71–3.2)	.280		
High	199 (26%)	0.73 (0.19–2.9)	.665		
Maternal smoking during pregnancy per day					
No	493 (65%)	1.0			
1-10	147 (20%)	0.71 (0.28–1.8)	.465		
≥10	112 (15%)	0.54 (0.15–1.9)	.346		
Hypertension before pregnancy	34 (5%)		1.000		
Epilepsy	4 (1%)		1.000		
Obstetric					
Multiple pregnancy	172 (23%)	1.9 (0.96–3.7)	.069	1.8 (0.86–3.7)	.119
Corticosteroids	131 (17%)	1.01 (0.44–2.3)	.983		
Gestational diabetes mellitus					
No	715 (95%)	1.0			
With diet	22 (3%)		1.000		
With insulin	16 (2%)		1.000		
Hypertension during pregnancy					
No	583 (77%)	1.0			
≥90 mm Hg	110 (15%)	0.52 (0.15–1.8)	.299		
Preeclampsia/eclampsia	60 (8%)	1.02 (0.34–3.0)	.973		
Prolonged rupture of membranes					
No	440 (58%)	1.0			
<1-11 h	127 (17%)	0.70 (0.26–1.9)	.489		
12-24 h	28 (4%)	0.89 (0.12–6.4)	.906		
1-7 d	106 (14%)	0.89 (0.37–2.2)	.801		
>7 d	53 (7%)	0.54 (0.12–2.4)	.413		

Teune. Perinatal risk indicators for long-term neurological morbidity. Am J Obstet Gynecol 2011. *(continued)*

TABLE 4
Risk indicators for neurological morbidity (5 years); infants with a major handicap vs infants with no or minor handicap *(continued)*

Candidate predictors	No. of children (pooled)	Univariable analysis (pooled) Crude odds ratio (95% CI)	*P* value	Multivariable analysis (pooled) Adjusted odds ratio (95% CI)	*P* value
Meconium stained fluid	41 (5%)	1.5 (0.48–4.9)	.475	2.4 (0.70–8.0)	.167
Presentation: other than vertex	231 (31%)	0.73 (0.36–1.5)	.390		
Neonatal					
Gestational age, wk		0.98 (0.83–1.2)	.805		
25-28	108 (14%)				
28-30	219 (29%)				
30-32	320 (43%)				
32-34	106 (14%)				
Low birthweight (<10th percentile)	197 (26%)	1.1 (0.55–2.2)	.797		
Male sex	396 (53%)	2.9 (1.2–7.4)	.033	3.0 (1.1–8.0)	.040
Asphyxia	71 (9%)	1.5 (0.48–4.7)	.488		
Bronchopulmonary dysplasia	112 (15%)	2.2 (0.82–5.6)	.138		
Respiratory distress syndrome					
No	421 (56%)	1.0			
Clinical	111 (15%)	2.3 (1.02–5.2)	.046		
Radiographic	221 (29%)	1.3 (0.58–2.7)	.566		
Pneumothorax	50 (7%)	1.5 (0.49–4.3)	.505		
Seizures					
No	724 (96%)	1.0		1.0	
First d	4 (1%)	7.2 (0.68–75.9)	.101	9.3 (0.84–103.6)	.069
≥2 d	26 (3%)	7.4 (2.8–19.3)	.000	5.8 (1.9–17.9)	.003
Intracranial hemorrhage					
No	653 (87%)	1.0		1.0	
Suspect	41 (5%)	2.3 (0.72–7.0)	.165	1.1 (0.29–4.0)	.917
Proven	58 (8%)	3.4 (1.5–7.7)	.004	2.6 (1.02–6.8)	.045
Necrotizing enterocolitis	42 (6%)		.998		
Hyperbilirubinemia ≥200 μmol/L	212 (28%)	1.8 (0.96–3.5)	.066	1.8 (0.87–3.6)	.115
Sepsis (culture proven)	78 (10%)	1.3 (0.50–3.5)	.573		
Continuous positive airway pressure, d	mean = 2 days	1.03 (0.97–1.09)	.312		
Artificial ventilation, d	mean = 3 days	1.02 (0.99–1.05)	.224		

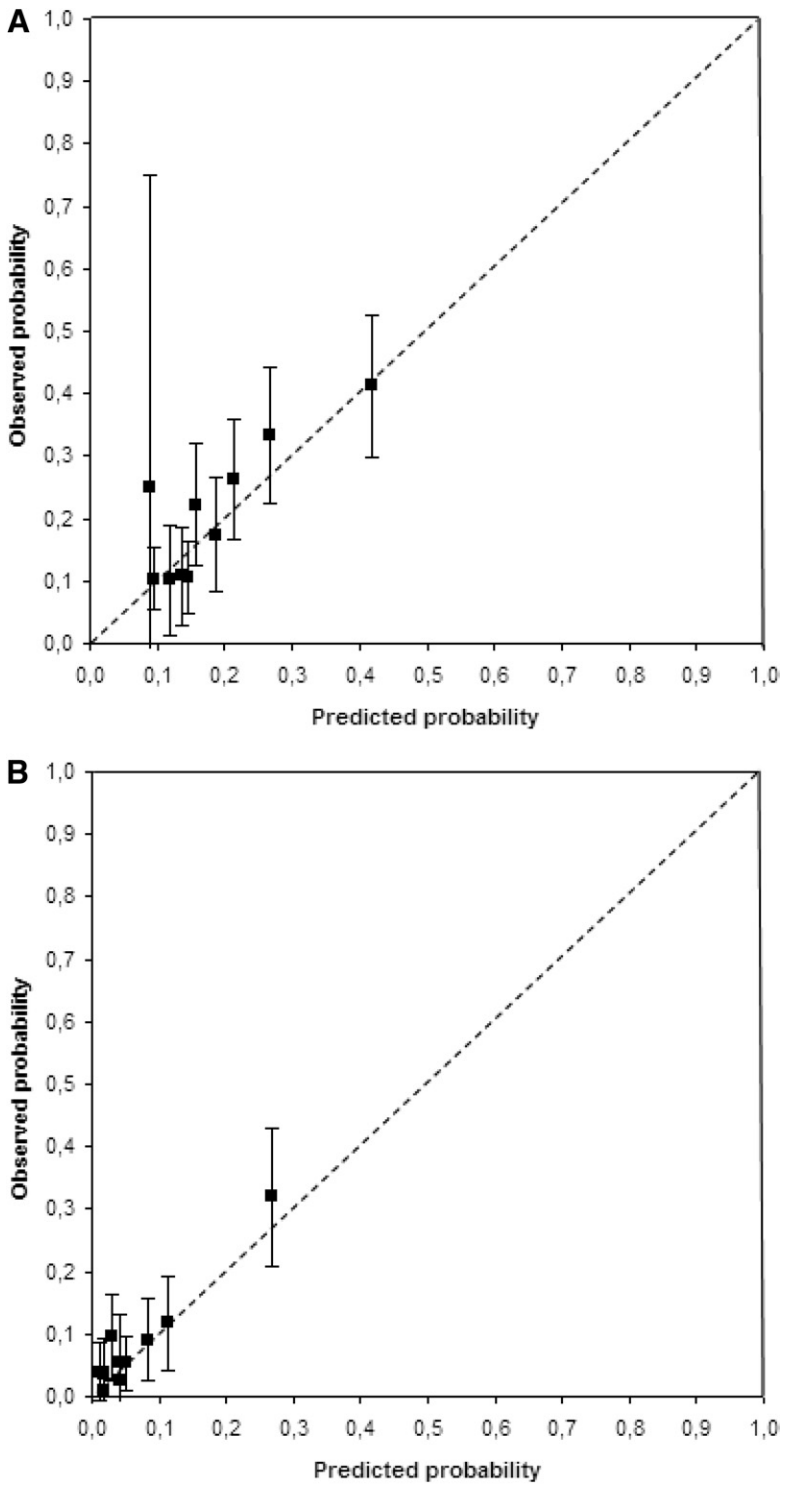
CI, confidence interval.

Teune. Perinatal risk indicators for long-term neurological morbidity. Am J Obstet Gynecol 2011.

cause the Gesell test and Denver development test were assessed for screening of cognitive and behavioral problems at 2 and 5 years of age, respectively. Although these tests are good in the detection of severe developmental problems, these tests have been criticized as unreliable in predicting less severe or specific problems.

Another limitation is that cranial ultrasound scans were performed in only 6 of the 8 neonatal intensive care units in The Netherlands in 1983, which probably caused an underestimation of the prevalence of intracranial hemorrhage. This is further strengthened by the fact that periventricular leukomalacia was not yet diagnosed at that time. Nevertheless, intracranial hemorrhage is a strong risk indicator for long-term neurologic morbidity in the POPS cohort. The same

FIGURE 1
Calibration plot at 2 years



A, Infants with minor/major handicap vs with no handicap. **B,** Infants with major handicap vs infants with no or minor handicap.

Teune. Perinatal risk indicators for long-term neurological morbidity. Am J Obstet Gynecol 2011.

finding is found in other studies, such as the EPIPAGE (Etude Epidemiologique sur les Petits Ages Gestationnels) cohort.[23]

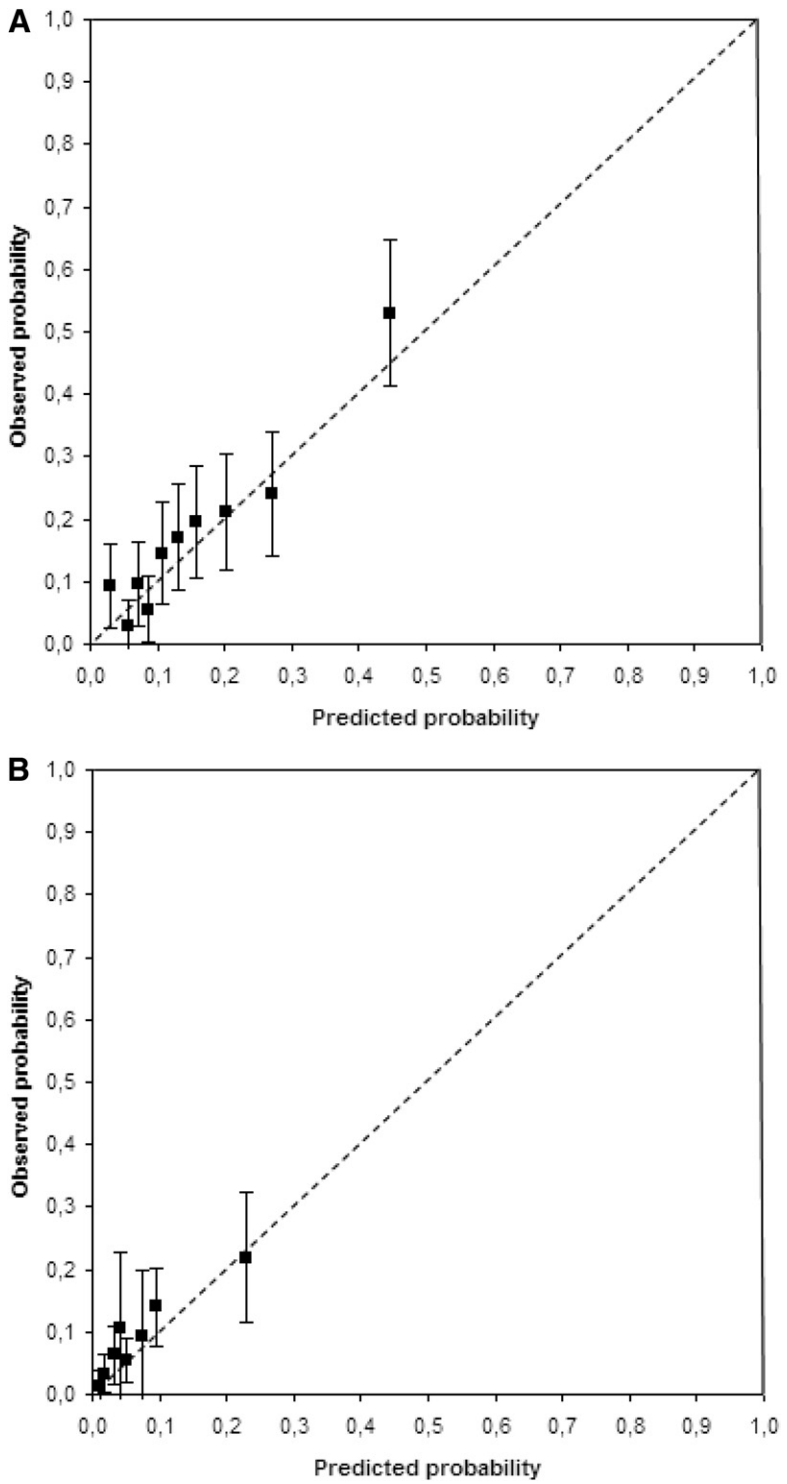
Overall, male sex, intracranial hemorrhage, and seizures seemed important risk indicators for the development of a handicap at 2 and 5 years of age in surviving infants. In our models, asphyxia was not a significant risk indicator for the occurrence of minor or major handicaps. The theory that asphyxia is the main underlying cause of cerebral palsy has also been challenged previously by Nelson,[6] who showed that perinatal asphyxia accounts for only a small proportion of the cases of cerebral palsy, whereas neurologic morbidity often follows the presence of multiple risk indicators later in life.

In the model for neurologic morbidity at 2 years of age (comparison of infants with major handicap with infants with no or minor handicap), maternal smoking was associated with a decreased risk for neurologic morbidity. We do not have an explanation for this result.

Neurologic morbidity is not only an enormous burden for the individual infant and their parents but also for society. As a consequence, multiple multicenter studies are performed nowadays to search for interventions that can prevent the incidence and severity of neurologic morbidity.

With the help of these prediction models of long-term neurologic morbidity, future obstetric studies can predict long-term outcomes when follow-up evaluation is not feasible. Modeling has several advantages. It can be inexpensive, free of ethical concerns over renewed approach of patients and fast; a computer model can simulate in minutes while follow up lasts years. Modeling has some less obvious benefits too because the process of constructing the model promotes systematic thought and generates insights about the nature of its components and how they interact, which may help to identify areas in which empiric research is most needed, may help generate new epidemiologic or clinical hypotheses, and may help to produce novel ideas for useful interventions. Of course, modeling also has limitations. Despite model theory or logic, inaccuracies in model parameters

FIGURE 2
Calibration plot at 5 years



A, Infants with minor/major handicap vs with no handicap. **B,** Infants with major handicap vs no or minor handicap.

Teune. Perinatal risk indicators for long-term neurological morbidity. Am J Obstet Gynecol 2011.

or omission of key factors can invalidate results.[24]

Before our prediction that models can be used in future obstetric studies to extrapolate the short-term neonatal outcomes to a longer study horizon, the models should be validated in more recent cohorts to investigate whether the same risk indicators for neurologic morbidity are found. Subsequently, these risk indicators could be recommended as primary endpoints in future obstetric studies.

In this cohort, male sex, intracranial hemorrhage, and seizures seem important risk indicators for neurologic morbidity at 2 and 5 years of age. This study shows that the development of prediction models for long-term neurologic morbidity is possible; however, our findings should be confirmed in more recent cohorts. ■

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