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Perinatal risk-indicators for long-term respiratory morbidity among preterm or very low birth weight neonates

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ABSTRACT

Objectives: To develop prediction models for long-term respiratory morbidity. To explore if respiratory distress syndrome (RDS) is a risk-indicator for long-term respiratory morbidity and to identify other perinatal risk-indicators for long-term respiratory morbidity.
Study design: In the Dutch POPS cohort 1338 live born infants delivered in The Netherlands in 1983, either before 32 completed weeks gestation and/or with a birth weight below 1500 g, were followed prospectively. We used multivariable logistic regression analyses to construct three prediction models for respiratory morbidity at 2, 5 and 19 years of age.
Results: At 2 years of age, maternal smoking (adjusted OR 1.5, 95% CI 1.0–2.4), prolonged rupture of membranes (adjusted OR 2.3, 95% CI 1.3–4.1), pre-eclampsia (adjusted OR 1.9, 95% CI 1.1–4.1), male gender (adjusted OR 1.5, 95% CI 1.1–2.0) and BPD (adjusted OR 1.9, 95% CI 1.1–3.2) were significantly associated with respiratory morbidity. Prolonged rupture of membranes (adjusted OR 3.7, 95% CI 1.6–8.5), family history of asthma (adjusted OR 5.9, 95% CI 2.7–13.0) and BPD (adjusted OR 1.8, 95% CI 1.1–3.0) were significantly associated with respiratory morbidity at 5 years of age. At 19 years of age only higher social class was associated with decreased respiratory morbidity (adjusted OR 0.64, 95% CI 0.41–0.99). The areas under the curves (AUC) were 0.65, 0.71 and 0.61 respectively. The prediction models for respiratory morbidity at 2 and 5 years of age showed a good calibration, while the calibration plot for respiratory morbidity at 19 year was less optimal.
Conclusions: RDS is not a risk-indicator for long-term respiratory morbidity at 2, 5 and 19 years in this cohort (OR 1.2, 95% 0.88–1.7; 1.3, 95% 0.88–2.0; OR 0.91, 95% 0.56–1.5 respectively). Future obstetric studies interested in the effect of a specific perinatal intervention on long-term respiratory morbidity, should consider taking bronchopulmonary dysplasia (BPD) as primary outcome instead of RDS.

1. Introduction

Many obstetrical 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. However, long-term follow-up is time-consuming, beyond obstetricians' awareness, expensive and falls outside the funding-period of most obstetric studies. Consequently, obstetrical interventions are usually not evaluated for their long-term outcomes.

A possibility to overcome this problem would be to develop prediction models for long-term outcomes, based on short-term outcomes and relevant covariates. The development of such models requires a longitudinal approach, in which data surrounding pregnancy, delivery and short-term outcomes are available, as well as follow-up data on various health related outcomes.

The Dutch POPS cohort (project on preterm and small for gestational age infants) is one of the few birth cohorts with a systematic assessment of these data. Data of infants born alive with a gestational age below 32 completed weeks and/or with a birth weight of 1.500 g were collected prospectively [1–3].

Literature on long-term outcome of respiratory health is limited, but high rates of respiratory morbidity have been reported

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in survivors born prematurely [4]. One important short-term neonatal complication is the occurrence of respiratory distress syndrome (RDS) which becomes manifest mainly in preterm infants. Fortunately, most infants recover from RDS. However, in infants with a birth weight between 500 and 1500 g, 3–43% develop chronic lung disease, also called bronchopulmonary dysplasia (BPD) which is a known risk factor for long-term respiratory morbidity [5,6].

The aim of this study is to explore if RDS is a risk-indicator for long-term respiratory morbidity and to identify other perinatal risk-indicators for long-term respiratory morbidity. Thereafter, we will use these risk-indicators to develop prediction models for long-term respiratory morbidity at 2, 5 and 19 years of age.

2. Materials and methods

2.1. Study design

For the development of prediction models for long-term respiratory morbidity, we used data available from a Dutch cohort study of preterm and/or small for gestational age infants (POPS study). All live born infants, delivered in The Netherlands between January and December 1983, either before 32 completed weeks of gestation and/or with a birth weight of less than 1500 g, were included in this cohort. The study ultimately consisted of 1338 infants, constituting 94% of the eligible infants born in 1983 in the Netherlands. Respiratory follow-up assessments were done at 2, 5 and 19 years of age [1–3].

The follow-up until the age of 2 years was carried out by local paediatricians all over The Netherlands. A standardised questionnaire was used to record information on respiratory problems at 24 months of corrected age. At 5 years chronological age a follow-up program was carried out by three specially trained paediatricians during a visit at home. At 19 years the European Community Respiratory Health Survey (ECRHS) questionnaire was mailed to the participants [7].

2.2. Outcomes

End-points used for this prediction model were respiratory morbidity at 2, 5 and 19 years of age. Respiratory morbidity at 2 years of age was defined as the occurrence of one or more of the following respiratory tract problems: recurrent upper respiratory tract infections, recurrent lower respiratory tract infections or other chronic lung diseases. Recurrent was defined as two or more upper or lower respiratory infections each year diagnosed by a physician. Other chronic lung diseases included asthma and chronic bronchitis.

For the respiratory morbidity at 5 years of age a composite score was derived from multiple variables related to respiratory complaints. By using categorical principal components analysis, the dimensionality of a dataset consisting of al large number of interrelated variables is reduced, while retaining as much as possible of the variation present in the database. In our analysis, the original set of 10 variables was reduced to two principal components. One principal component was associated with more chronic symptoms (throat infections, wheezing, bronchitis, asthma, shortness of breath, tightness of chest, subglottic laryngitis and pneumonia), the other with more incidental symptoms (colds and coughing). The principal component reflecting chronic morbidity was used as outcome for respiratory morbidity at 5 years of age. This principal component explains 41% of the original variability. All infants were categorised in two groups; infants with no or only mild respiratory complaints and infants with more serious respiratory complaints. Infants with a principal component score above the 85th percentile were categorised as infants with the most serious respiratory complaints and were used as end-point in our prediction model.

A similar analysis was done for respiratory morbidity at 19 years of age. In our analysis, the original set of 7 variables was reduced to two principal components. One principal component was associated with hay fever, eczema, asthma and complaints of wheezing any time in the last twelve months. The second principal component at 19 years of age was associated with shortness of breath when hurrying on level ground, when walking with other people on level ground and/or when walking at your own pace on level ground. Again the first principal component was used as outcome for respiratory morbidity at 19 years of age. This principal component explains 31% of the original variability. Infants with a principal component score above the 85th percentile were used as end-point in our prediction model.

2.3. Prognostic predictors

Candidate predictors for respiratory morbidity were determined based on existing literature of perinatal predictors for long-term respiratory morbidity, combined with consulting experts in the field. The following candidate predictors were included in the analysis: social class determined at 5 years of age, ethnicity, hypertension before pregnancy, pregnancy induced hypertension (diastolic pressure >90 mmHg), pre-eclampsia/eclampsia, diabetes mellitus, gestational diabetes, multiple pregnancy, vertex or other presentation, prolonged rupture of membranes, meconium stained fluid, glucocorticosteroids, caesarean section, small for gestational age (<10th percentile) [8], gestational age, gender, neonatal asphyxia, lung problems in the neonatal period (respiratory distress syndrome, bronchopulmonary dysplasia, pneumonia, pneumothorax, lung emphysema), duration of mechanical ventilation (continuous or intermittent), maternal smoking habits and a positive family history of asthma. Neonatal asphyxia was defined as low fifth minute Apgar score (<7) and/or umbilical cord acidosis (pH < 7.05). Respiratory distress syndrome was defined as the need for extra O2 > 24 h, expiratory grunting, tachypnoea, sternal an intercostal retractions and nasal flaring (clinical diagnosis) and/or typical X-ray abnormalities (radiographic diagnosis). 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) [9].

2.4. Statistical analysis

We developed three multivariable logistic regression models in which we analysed the association between the candidate predictors and respiratory morbidity at 2, 5 and 19 years of age, respectively. Multiple imputations were used to adjust for missing values. We created five imputed datasets, based on the candidate predictors mentioned above and all available outcome specific data at 2, 5 and 19 years of age. Uncertainty about imputed values is reflected in differences between different imputed datasets, and incorporated in the estimated standard errors and associated *P*-values for the pooled model. Software used for the imputation was SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The imputation method in SPSS is largely based on the chained equations approach in MICE [10,11].

The prevalence of the candidate predictors was first analysed. Subsequently, a univariable and multivariable regression analysis was performed to estimate odds ratios (ORs), 95% confidence intervals (95% CI) and corresponding *P*-values for dichotomous and continuous variables.

As the use of too stringent *P*-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 [12]. Furthermore, we used a stepwise backward selection

procedure, using a predefined significance level of >20% for removing variables from the models [13]. Variables that remained in the last step of the backward selection procedure in at least 4 of the 5 datasets were included in the final logistic regression analysis. The discriminative capacity of the models was evaluated by calculating the area under the curve. Calibration of the models was assessed by comparing the calculated probabilities with the observed proportion of respiratory morbidity. The goodness-of-fit was tested formally with the Hosmer and Lemeshow test statistic. All data were analysed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Sample and respiratory morbidity incidence

Of the original cohort of 1.338 infants, 1143 infants survived the first 48 h after birth, 1.026 infants survived the neonatal period

Table 1
Results of the uni- and multivariable analysis for respiratory morbidity at 2 years of age (n = 959).

Candidate predictors	N (%) of infants or mean after imputation	N (%) of infants or mean before imputation	Univariable analysis		Multivariable analysis	
			Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Environmental factors						
Ethnicity						
Both parents Caucasian	814 (85%)	812 (85%)	0.93 (0.63–1.4)	0.737		
One/both parent(s) Mediterranean	55 (6%)	54 (6%)	1.2 (0.66–2.4)	0.501		
One/both parent (s) African	40 (4%)	38 (4%)	0.77 (0.36–1.7)	0.499		
One/both parent(s) Asian	43 (4%)	42 (4%)	1.4 (0.72–2.6)	0.340		
Other	7 (1%)	7 (1%)				
Social class						
Low	386 (40%)	310 (41%)	1.0			
Moderate	348 (36%)	274 (37%)	0.77 (0.55–1.09)	0.141		
High	225 (24%)	165 (22%)	0.88 (0.59–1.3)	0.539		
Maternal smoking during pregnancy						
No	626 (65%)	569 (66%)	1.0		1.0	
1–10 cig/day	186 (19%)	168 (19%)	0.92 (0.63–1.3)	0.656	0.86 (0.59–1.27)	0.458
≥10 cig/day	147 (15%)	128 (15%)	1.5 (1.02–2.2)	0.040	1.5 (1.00–2.4)	0.050
Hypertension before pregnancy	44 (5%)	43 (5%)	0.23 (0.08–0.65)	0.005	0.32 (0.11–0.94)	0.009
Asthma in the family						
No	424 (44%)	410 (45%)	1.0			
One side of the family	399 (42%)	388 (42%)	1.03 (0.74–1.4)	0.860		
Both sides of the family	136 (14%)	117 (13%)	1.07 (0.64–1.8)	0.796		
Obstetric						
Multiple pregnancy	199 (21%)	199 (21%)	1.4 (0.98–2.0)	0.067	1.3 (0.92–1.9)	0.127
Corticosteroids	151 (16%)	150 (16%)	1.02 (0.69–1.5)	0.940		
Gestational diabetes						
No	917 (96%)	915 (96%)	1.0			
With diet	23 (2%)	23 (2%)	2.1 (0.92–4.8)	0.079		
With insulin	19 (2%)	19 (2%)	0.64 (0.20–2.1)	0.455		
Hypertension during pregnancy						
No	698 (73%)	696 (73%)	1.0		1.0	
≥90 mm Hg	176 (18%)	174 (18%)	0.57 (0.38–0.84)	0.005	1.0 (0.63–1.6)	0.983
Preeclampsia/eclampsia	85 (9%)	85 (9%)	0.96 (0.58–1.6)	0.859	1.9 (1.05–3.3)	0.033
Prolonged rupture of membranes						
No	593 (62%)	590 (62%)	1.0		1.00	
<1–12 h	158 (17%)	157 (17%)	1.3 (0.89–1.9)	0.166	1.1 (0.76–1.7)	0.531
12–24 h	32 (3%)	31 (3%)	1.6 (0.72–3.5)	0.247	1.5 (0.65–3.3)	0.351
1–7 days	113 (12%)	112 (12%)	1.7 (1.07–2.7)	0.026	1.5 (0.91–2.4)	0.113
>7 days	62 (6%)	62 (6%)	2.6 (1.5–4.4)	0.001	2.3 (1.3–4.1)	0.005
Meconium stained fluid	68 (7%)	64 (7%)	1.2 (0.67–2.0)	0.589		
Caesarean section	456 (48%)	456 (48%)	0.80 (0.60–1.07)	0.138		
Presentation						
Other than vertex	293 (31%)	293 (31%)	1.1 (0.82–1.5)	0.497		
Neonatal						
Gestational age			0.92 (0.87–0.98)	0.007		
25–28 weeks	117 (12%)	117 (12%)				
28–30 weeks	242 (25%)	241 (25%)				
30–32 weeks	345 (36%)	344 (36%)				
>32 weeks	256 (27%)	255 (27%)				
Low birth weight (<p10)	357 (37%)	356 (37%)	0.65 (0.48–0.87)	0.004	0.75 (0.53–1.06)	0.100
Male gender	489 (51%)	489 (51%)	1.5 (1.09–2.0)	0.012	1.5 (1.07–2.0)	
Asphyxia	89 (9%)	69 (8%)	1.3 (0.76–2.2)	0.362		
BPD	133 (14%)	81 (10%)	2.1 (1.2–3.4)	0.011	1.9 (1.1–3.2)	
RDS						
No	586 (61%)	586 (61%)	1.0			
Clinical	126 (13%)	126 (13%)	1.01 (0.65–1.6)	0.965		
Radiographic	247 (26%)	247 (21%)	1.2 (0.88–1.7)	0.236		
Pneumonia	59 (6%)	59 (6%)	1.3 (0.71–2.2)	0.445		
Pneumothorax	54 (6%)	54 (6%)	1.8 (0.99–3.2)	0.056		
Interstitional emphysema	47 (5%)	47 (5%)	1.6 (0.86–3.0)	0.141		
CPAP (days)	2.0	1.9	1.01 (0.98–1.04)	0.405		
Artificial ventilation (days)	3.2	3.1	1.01 (0.99–1.03)	0.242		

Abbreviations BPD = bronchopulmonary dysplasia RDS = respiratory distress syndrome CPAP = continuous positive airway pressure.

(>28 days), 969 infants were alive at 2 years of age, 966 infants at 5 years of age and 959 infants survived to the age of 19. At 2 years of age information on respiratory morbidity was missing for 97 infants (follow-up rate 90%). At 5 years of age information on respiratory morbidity was missing for 39 infants (follow-up rate 96%). At 19 years information on respiratory morbidity was available for 690 infants (follow-up rate 72%).

The rate of infants with respiratory problems at 2 years of age was 24% for imputation and 30% after imputation. This rate was 15% (n = 143 infants) at 5 years of age and 16% (n = 155 infants) at 19 years of age after imputation.

3.2. Univariable and multivariable models: respiratory morbidity at 2 years of age

Table 1 shows the results of the univariable and multivariable regression analysis for respiratory morbidity at 2 years of age. Maternal smoking (>10 cig/day) (adjusted OR 1.5; 95% CI 1.0–2.4),

Table 2
Results of the uni- and multivariable analysis for respiratory morbidity at 5 years of age (n = 959).

Candidate predictors	N (%) of infants or mean after imputation	N (%) of infants or mean before imputation	Univariable analysis		Multivariable analysis	
			Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Environmental factors						
Ethnicity						
Both parents Caucasian	814 (85%)	812 (85%)	1.1 (0.68–1.9)	0.636		
One/both parent(s) Mediterranean	55 (6%)	54 (6%)	1.1 (0.52–2.4)	0.803		
One/both parent (s) African	40 (4%)	38 (4%)	1.5 (0.66–3.3)	0.346		
One/both parent(s) Asian	43 (4%)	42 (4%)	0.42 (0.13–1.4)	0.151		
Other	7 (1%)	7 (1%)				
Social class						
Low	386 (40%)	310 (41%)	1.0			
Moderate	348 (36%)	274 (37%)	1.1 (0.68–1.7)	0.755		
High	225 (24%)	165 (22%)	0.68 (0.32–1.4)	0.321		
Maternal smoking during pregnancy						
No	626 (65%)	569 (66%)	1.0			
1–10 cig/day	186 (19%)	168 (19%)	1.2 (0.76–2.0)	0.387		
≥10 cig/day	147 (15%)	128 (15%)	1.6 (0.96–2.6)	0.070		
Hypertension before pregnancy	44 (5%)	43 (5%)	0.40 (0.12–1.3)	0.132		
Asthma in the family						
No	424 (44%)	410 (45%)	1.0			
One side of the family	399 (42%)	388 (42%)	2.3 (1.1–4.9)	0.057	2.4 (1.09–5.1)	0.057
Both sides of the family	136 (14%)	117 (13%)	5.7 (2.6–12.7)	0.001	5.9 (2.7–13.0)	0.001
Obstetric						
Multiple pregnancy	199 (21%)	199 (21%)	0.87 (0.55–1.4)	0.551		
Corticosteroids	151 (16%)	150 (16%)	1.03 (0.63–1.7)	0.916		
Gestational diabetes						
No	917 (96%)	915 (96%)	1.0			
With diet	23 (2%)	23 (2%)	0.25 (0.03–1.9)	0.179		
With insulin	19 (2%)	19 (2%)	1.02 (0.29–3.6)	0.971		
Hypertension during pregnancy						
No	698 (73%)	696 (73%)	1.0			
≥90 mm Hg	176 (18%)	174 (18%)	0.78 (0.48–1.3)	0.321		
Preeclampsia/eclampsia	85 (9%)	85 (9%)	0.96 (0.51–1.8)	0.900		
Prolonged rupture of membranes						
No	593 (62%)	590 (62%)				
<1–12 h	158 (17%)	157 (17%)	1.04 (0.62–1.7)	0.889	1.1 (0.67–2.0)	0.631
12–24 h	32 (3%)	31 (3%)	3.1 (1.4–6.9)	0.005	3.7 (1.6–8.5)	0.003
1–7 days	113 (12%)	112 (12%)	1.5 (0.83–2.5)	0.194	1.4 (0.75–2.5)	0.313
>7 days	62 (6%)	62 (6%)	2.0 (1.0–3.7)	0.038	1.8 (0.92–3.5)	0.086
Meconium stained fluid	68 (7%)	64 (7%)	0.96 (0.47–2.0)	0.909		
Caesarean section	456 (48%)	456 (48%)	0.71 (0.50–1.0)	0.065		
Presentation						
Other than vertex	293 (31%)	293 (31%)	0.65 (0.43–0.98)	0.041		
Neonatal						
Gestational age			0.94 (0.88–1.0)	0.109		
25–28 weeks	117 (12%)	117 (12%)				
28–30 weeks	242 (25%)	241 (25%)				
30–32 weeks	345 (36%)	344 (36%)				
>32 weeks	256 (27%)	255 (27%)				
Low Birth weight (<p10)	357 (37%)	356 (37%)	0.78 (0.53–1.1)			
Male gender	489 (51%)	489 (51%)	1.5 (1.03–2.1)	0.035	1.4 (0.96–2.1)	0.076
Asphyxia	89 (9%)	69 (8%)	1.3 (0.63–2.6)			
BPD	133 (14%)	81 (10%)	1.9 (1.2–3.1)	0.012	1.8 (1.07–3.0)	0.028
RDS						
No	586 (61%)	586 (61%)	1.0			
Clinical	126 (13%)	126 (13%)	0.88 (0.50–1.6)	0.667		
Radiographic	247 (26%)	247 (21%)	1.3 (0.88–2.0)	0.182		
Pneumonia	59 (6%)	59 (6%)	1.5 (0.77–2.9)	0.235		
Pneumothorax	54 (6%)	54 (6%)	1.5 (0.75–3.0)	0.249		
Interstitional emphysema	47 (5%)	47 (5%)	2.0 (1.03–4.0)	0.040		
CPAP (days)	2.0	1.9	1.03 (0.99–1.06)	0.124		
Artificial ventilation (days)	3.2	3.1	1.02 (1.0–1.04)	0.667		

Abbreviations BPD = bronchopulmonary dysplasia RDS = respiratory distress syndrome CPAP = continuous positive airway pressure.

prolonged rupture of membranes (>7 days) (adjusted OR 2.3; 95% CI 1.3–4.1), pre-eclampsia/eclampsia (adjusted OR 1.9; 95% CI 1.1–3.3), male gender (adjusted OR 1.5; 95% CI 1.1–2.0) and the occurrence of BPD (adjusted OR 1.9; 95% CI 1.1–3.2) were significantly associated with respiratory morbidity at 2 years of age. Hypertension before pregnancy was associated with decreased risk for respiratory morbidity (adjusted OR 0.32; 95% C.I. 0.11–0.94).

3.3. Univariable and multivariable models: respiratory morbidity at 5 years of age

Table 2 shows the results of the univariable and multivariable regression analysis for respiratory morbidity at 5 years of age. Prolonged rupture of membranes (12–24 h) (adjusted OR 3.7; 95% CI 1.6–8.5), the occurrence of asthma in both sides of the family (adjusted OR 5.9; 95% CI 2.7–13.0) and the occurrence of BPD

Table 3
Results of the uni- and multivariable analysis for respiratory morbidity at 19 years of age ($n = 959$).

Candidate predictors	*N* (%) of infants or mean after imputation	*N* (%) of infants or mean before imputation	Univariable analysis		Multivariable analysis	
			Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Environmental factors						
Ethnicity						
Both parents Caucasian	814 (85%)	812 (85%)	0.39 (0.16–0.95)	0.080		
One/both parent(s) Mediterranean	55 (6%)	54 (6%)	2.5 (1.1–5.6)	0.036		
One/both parent (s) African	40 (4%)	38 (4%)	3.0 (0.82–11.1)	0.137		
One/both parent(s) Asian	43 (4%)	42 (4%)	1.3 (0.29–5.8)	0.732		
Other	7 (1%)	7 (1%)				
Social class						
Low	386 (40%)	310 (41%)	1.0		1.0	
Moderate	348 (36%)	274 (37%)	0.63 (0.41–0.97)	0.040	0.64 (0.41–0.99)	0.048
High	225 (24%)	165 (22%)	0.52 (0.28–0.95)	0.043	0.54 (0.29–0.99)	0.059
Maternal smoking during pregnancy						
No	626 (65%)	569 (66%)	1.0		1.0	
1–10 cig/day	186 (19%)	168 (19%)	0.85 (0.49–1.5)	0.567	0.78 (0.44–1.4)	0.400
≥10 cig/day	147 (15%)	128 (15%)	1.7 (0.92–3.2)	0.108	1.6 (0.85–3.0)	0.162
Hypertension before pregnancy	44 (5%)	43 (5%)	0.38 (0.10–1.5)	0.176	0.39 (0.10–1.5)	0.177
Asthma in the family						
No	424 (44%)	410 (45%)	1.0			
One side of the family	399 (42%)	388 (42%)	0.87 (0.54–1.4)	0.588		
Both sides of the family	136 (14%)	117 (13%)	0.91 (0.31–2.7)	0.875		
Obstetric						
Multiple pregnancy	199 (21%)	199 (21%)	0.92 (0.46–1.8)	0.806		
Corticosteroids	151 (16%)	150 (16%)	1.2 (0.70–2.0)	0.527		
Gestational diabetes						
No	917 (96%)	915 (96%)	1.0			
With diet	23 (2%)	23 (2%)	1.03 (0.15–6.8)	0.978		
With insulin	19 (2%)	19 (2%)	0.92 (0.20–4.2)	0.910		
Hypertension during pregnancy						
No	698 (73%)	696 (73%)	1.0			
≥90 mm Hg	176 (18%)	174 (18%)	0.82 (0.48–1.4)	0.453		
Preeclampsia/eclampsia	85 (9%)	85 (9%)	0.91 (0.35–2.4)	0.848		
Prolonged rupture of membranes						
No	593 (62%)	590 (62%)	1.0			
<1–12 h	158 (17%)	157 (17%)	0.85 (0.44–1.6)	0.632		
12–24 h	32 (3%)	31 (3%)	2.1 (0.92–4.9)	0.076		
1–7 days	113 (12%)	112 (12%)	1.2 (0.65–2.3)	0.531		
> 7 days	62 (6%)	62 (6%)	1.08 (0.49–2.4)	0.854		
Meconium stained fluid	68 (7%)	64 (7%)	0.68 (0.26–1.8)	0.446		
Caesarean section	456 (48%)	456 (48%)	0.79 (0.51–1.2)	0.284		
Presentation						
Other than vertex	293 (31%)	293 (31%)	0.92 (0.53–1.6)	0.791		
Neonatal						
Gestational age			1.00 (0.92–1.1)	0.970		
25–28 weeks	117 (12%)	117 (12%)				
28–30 weeks	242 (25%)	241 (25%)				
30–32 weeks	345 (36%)	344 (36%)				
>32 weeks	256 (27%)	255 (27%)				
Low Birth weight (<p10)	357 (37%)	356 (37%)	0.77 (0.48–1.2)	0.274		
Male gender	489 (51%)	489 (51%)	1.06 (0.58–1.9)	0.860		
Asphyxia	89 (9%)	69 (8%)	1.2 (0.59–2.6)	0.582		
BPD	133 (14%)	81 (10%)	0.94 (0.44–2.0)	0.876		
RDS						
No	586 (61%)	586 (61%)	1.0			
Clinical	126 (13%)	126 (13%)	0.73 (0.37–1.4)	0.360		
Radiographic	247 (26%)	247 (21%)	0.91 (0.56–1.5)	0.723		
Pneumonia	59 (6%)	59 (6%)	0.46 (0.04–5.8)	0.575		
Pneumothorax	54 (6%)	54 (6%)	0.47 (0.12–1.9)	0.312		
Interstitional emphysema	47 (5%)	47 (5%)	0.40 (0.06–2.8)	0.375		
CPAP (days)	2.0	1.9	1.01 (0.94–1.08)	0.808		
Artificial ventilation (days)	3.2	3.1	1.00 (0.93–1.06)	0.923		

Abbreviations BPD = bronchopulmonary dysplasia RDS = respiratory distress syndrome CPAP = continuous positive airway pressure.

(adjusted OR 1.8; 95% CI 1.1–3.0) were significantly associated with respiratory morbidity at 5 years of age.

3.4. Univariable and multivariable models: respiratory morbidity at 19 years of age

The results of the univariable and multivariable regression analysis are shown in Table 3. Only higher social class was significantly associated with decreased respiratory morbidity at 19 years of age (adjusted OR 0.64; 95% CI 0.41–0.99).

3.5. Model performance

The prediction models for respiratory morbidity at 2, 5 and 19 years of age discriminate modestly well between diseased and non-diseased with an area under the curve (AUC) of 0.65 (95% CI 0.61–0.68), 0.71 (95% CI 0.66–0.75) and of 0.61 (95% CI 0.56–0.66) respectively. The calibration plots for respiratory morbidity at 2, 5 and 19 years of age are shown in Fig. 1A–C. The prediction models for respiratory morbidity at 2 and 5 years of age show a good calibration, while the calibration plot for respiratory morbidity at

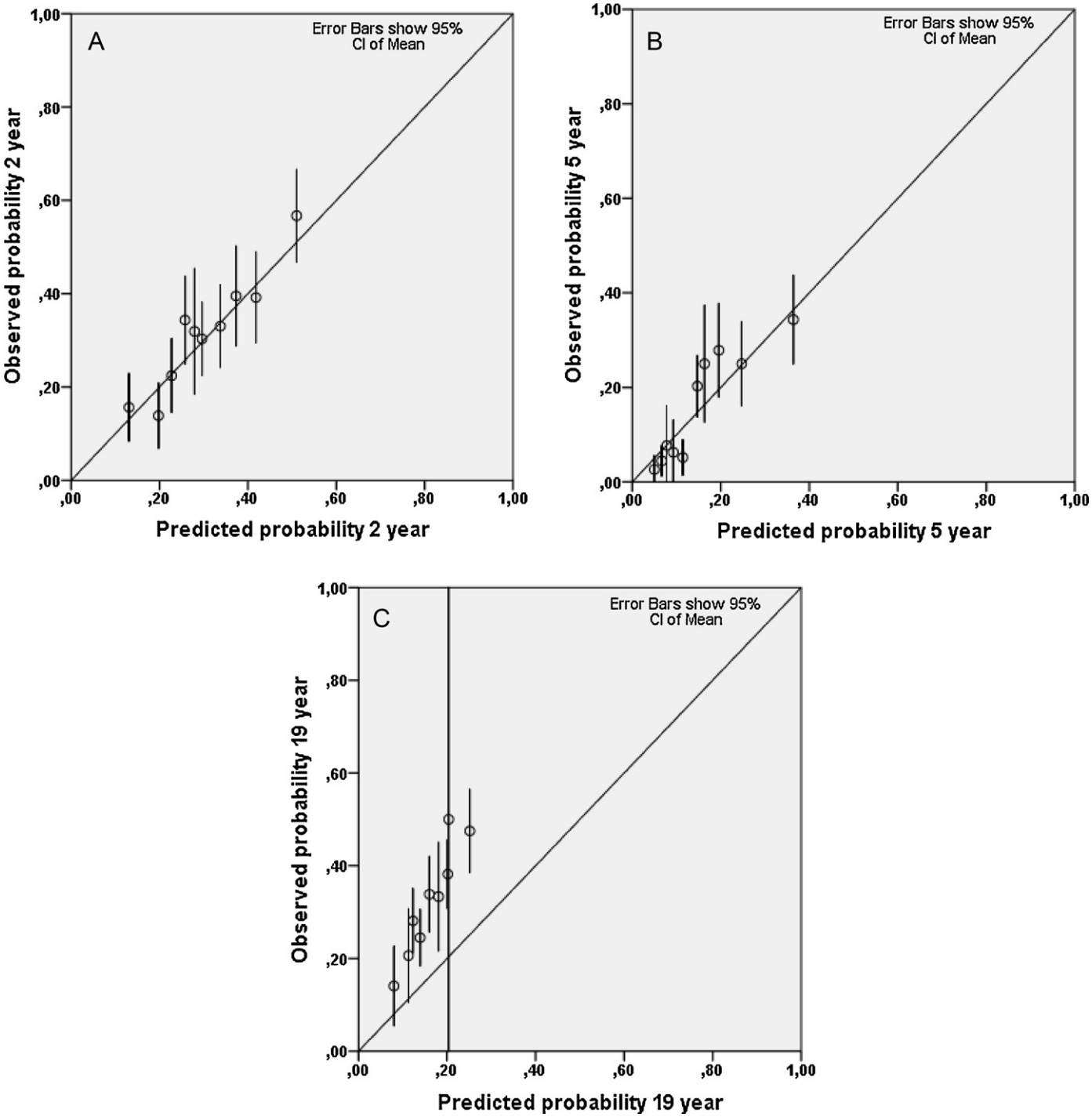

Fig. 1. (A) Calibration plot prediction model respiratory morbidity at 2 years of age. (B) Calibration plot prediction model respiratory morbidity at 5 years of age. (C) Calibration plot prediction model respiratory morbidity 19 years of age.

19 year is less optimal. The prediction model for respiratory morbidity at 19 years of age underestimates the risk for respiratory morbidity. The Hosmer–Lemeshow goodness-of-fit test was not significant for all three prediction models.

4. Comment

We developed three prediction models for respiratory morbidity at 2, 5 and 19 years of age for infants delivered, either before 32 completed weeks of gestation and/or with a birth weight of less than 1500 g. In this cohort RDS was not associated with respiratory morbidity at any of the three ages. The occurrence of prolonged rupture of membranes and bronchopulmonary dysplasia was significantly associated with respiratory morbidity at 2 and 5 years of age. Only social class was significantly associated with a decreased respiratory morbidity at 19 years of age. An explanation for these findings could be that perinatal factors decline in importance throughout childhood and other factors such as growth and development, social and familial factors and life events play a much greater role in the developing severe respiratory morbidity later in life.

With the help of these prediction models of long-term respiratory morbidity, future obstetric studies can predict long-term outcomes when follow-up is not feasible. Modelling 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. Of course, modelling has also limitations. Failings in model theory or logic, inaccuracies in model parameters, or omission of key factors can all invalidate results [14].

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 factors on long-term respiratory morbidity. Another strength is that this cohort was followed prospectively till the age of 19.

A limitation of this study is that the same outcome variables were not available at all three ages, so that a different approach had to be used to define respiratory morbidity at 2, 5 and 19 years of age.

Another limitation is that this cohort was born in 1983. Since that time the neonatal healthcare has changed substantially. The introduction of antenatal corticosteroids, surfactant therapy and the implementation of lung-protective strategies have increased survival rates and decreased the occurrence of respiratory morbidity of the neonate born at a specific gestational age. A comparison between a regional follow-up study (the Leiden Follow-Up Project on Prematurity (LFUPP) initiated in 1996–1997 ($n = 266$) and participants of the POPS study born in that same region in 1983 ($n = 102$) showed that the survival rate of RDS is increased over the years, but that this is associated with an increase in children with BPD from 6% in the 1980s to 19% in the 1990s [15]. Apparently, the prevalence of pulmonary sequelae in the neonatal perinatal period has not declined over the years, but occurs in more vulnerable and immature infants.

At present, many obstetric studies evaluating perinatal interventions that aim to improve fetal lung maturity, such as repeated doses of corticosteroids, are using RDS as primary end-point. However, the relation between RDS and long-term respiratory morbidity is not clear because long-term reports on respiratory health in infants born prematurely are limited and often contradictory. Based on this study, BPD seems a better predictor for respiratory problems later in life than RDS. By taking BPD as a primary end-point instead of RDS the overall verdict of a specific perinatal intervention may change substantially [16,17].

Another important observation of this study is the impact that prolonged ruptured membranes had on respiratory morbidity in later life. This observation could be an argument for induction of labour in women with preterm prelabour rupture of membranes. This subject is currently under study in two multicenter trials, and our analysis shows that both studies should follow their patients to evaluate the consequences of prolonged rupture of membranes between 34 and 37 weeks [18–20].

In this cohort RDS is not a risk-indicator for long-term respiratory morbidity. Future obstetric studies interested in the effect of a specific perinatal intervention on long-term respiratory morbidity, should consider taking BPD as primary outcome instead of RDS.

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