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Pediatric RESEARCH

POPULATION STUDY ARTICLE

Evaluating preterm care across Europe using the eNewborn European Network database

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BACKGROUND: The inefficiency of recording data repeatedly limits the number of studies conducted. Here we illustrate the wider use of data captured as part of the European eNewborn benchmarking programme.

METHODS: We extracted data on 39,529 live-births from 22 weeks 0 days to 31 weeks 6 days gestational age (GA) or ≤1500 g birth weight. We explored relationships between delivery room care and Apgar scores on mortality and bronchopulmonary dysplasia (BPD) and calculated the time needed for each country to detect a clinically relevant change in these outcomes following a hypothetical intervention.

RESULTS: Early neonatal, neonatal, and in-hospital mortality were 3.90% (95% CI 3.71, 4.09), 6.00% (5.77, 6.24) and 7.57% (7.31, 7.83), respectively. The odds of death were greater with decreasing GA, lower Apgar scores, growth restriction, male sex, multiple birth and no antenatal steroids. Relationships for BPD were similar. The time required for participating countries to achieve 80% power to detect a relevant change in outcomes following a hypothetical intervention in 23–25 weeks' GA infants ranged from 12 years for neonatal mortality and 22 years for BPD compared to 1 year for the whole network.

CONCLUSIONS: The eNewborn platform offers opportunity to drive efficiencies in benchmarking, quality control and research.

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INTRODUCTION

Very preterm, very low birth weight infants are major contributors to the population burden of mortality and morbidity related to perinatal factors; hence, efforts to improve the quality of care for this patient group is an important area of health service endeavour.[1] Data collection and analyses of processes and outcomes across neonatal units and networks are potentially informative and can be powerful tools to improve quality by benchmarking and feedback. Such data might also offer substantial potential for research.

There are, however, many practical challenges involved in utilising data from multiple countries to improve neonatal care. There are differences between and within countries in the methods used to record data, the regulatory approvals governing their use, consistency in the items recorded and their definitions, no less in clinical practice.[2] These difficulties can be major obstacles to realising their potential. In Europe, the open platform EuroNeoNet, was an initial attempt to record and utilise data from neonatal units.[3] EuroNeoNet closed in 2015 and was followed by eNewborn, a platform integrating innovative information technology, original software, a revision of the EuroNeoNet data set, and international collaboration. The characteristics of the eNewborn platform have been described elsewhere.[4]

The aim of this paper is to report a pilot evaluation of eNewborn as a large, real-world data set. We used selected variables and an exemplar statistical analysis to provide an indication of the potential utility of the eNewborn database. Our specific objectives were to use the eNewborn database to (i) present summary statistics for early, neonatal and in-hospital mortality by gestational age (GA); (ii) analyse the relationships between delivery room care and Apgar scores at 1 and 5 min on mortality and bronchopulmonary dysplasia (BPD) as a first step for the development of a future tool to predict risks of these outcomes in extremely and very low birth weight infants; and (iii) calculate the length of time that would be needed by individual countries on the basis of their neonatal admission rates to achieve 80% power to detect a clinically relevant change in mortality and BPD following a hypothetical intervention.

METHODS

Data source

The eNewborn database receives information on all live births born between 22 weeks 0 days and 31 weeks 6 days of gestation or ≤1500 g birth weight who are admitted to a participating neonatal unit. Data on babies who die in the delivery room are not included as information on these infants varies within and between countries. Over 200 neonatal units across Europe submit data to eNewborn. Belgium, Czech Republic, Portugal, Switzerland and the United Kingdom submit data extracted from an in-country database. Data are submitted by individual neonatal units from 5 additional countries: France 10 units, Germany 1 unit, Poland 1unit, Spain 2 units, and Finland 1 unit. Data entry was either directly online or as an extract from local electronic medical records. The proportional contribution of each country is described in Appendix 1.

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Definitions

We defined mortality as 'early' (days 0–6 from birth), 'neonatal' (days 0–27) and 'in-hospital' (before discharge from neonatal care) and BPD as any supplemental oxygen received at 36 weeks' postmenstrual age. We defined delivery room care as 'no resuscitation', 'basic resuscitation' (supplemental oxygen and/or positive pressure breaths with a bag and face mask or continuous positive airway pressure)' and 'advanced resuscitation' (endotracheal intubation and/or cardiac compression and/or administration of adrenaline/epinephrine). We categorised birth weight as extremely small for gestational age (ESGA; <3rd centile), small for gestational age (SGA; <10th centile) and appropriate for gestational age (AGA; ≥10th centile).[5]

Statistical analysis

We extracted 12 variables for each infant: (i) GA; (ii) birth weight; (iii) delivery room care (none, basic, advanced); (iv) Apgar at 1 min; (v) Apgar at 5 min; (vi) BPD (yes/no); (vii) death (early, neonatal, in-hospital; none); (viii) antenatal steroids (yes/no/partial); (ix) multiple birth (yes/no); (x) inborn/outborn; (xi) surfactant yes/no; (xii) sex. For each variable, we tabulated the number of infants and the number of missing values. As birth weights <250 g are implausible for liveborn infants, we classified these as missing. Major birth defects were recorded.

We estimated early neonatal, neonatal and in-hospital mortality for boys and girls combined and separately. To investigate the relationship between delivery room care and 1 and 5 min Apgar scores, we first explored their correlations by GA. We examined the evolution of Apgar scores by fitting an independence model to determine whether an association between 1 and 5 min values could be demonstrated. In case of a significant association, we tested the symmetry of the changes in these variables, presented as a square table, by Bowker's test.[6] In case of a significant test, we used the off-diagonal elements of the table to judge the direction in which the changes occurred. After the independence model, we fitted a model of linear by linear association to examine the effect of antenatal steroids on the Apgar score at 1 min. A finding of increasing Apgar scores with increasing compliance with antenatal steroid administration would reject the hypothesis of no association.[6]

We then conducted four exploratory logistic analyses. In the first analysis, we fitted 'neonatal mortality' as the endpoint against delivery room care category, GA, birth weight category, antenatal steroids, multiple birth and sex. To avoid problems of multicollinearity, we modelled birth weight category rather than birth weight. In the second analysis, we replaced delivery room care category with Apgar score at 1 min and in the third with Apgar score at 5 min. In addition, we fitted a similar model with the evolution of the Apgar score from minute 1 to minute 5, replacing delivery room care, Apgar scores at 1 min and at 5 min of the previous models. Similarly, we carried out a second series of three logistic regressions this time with BPD as the outcome and adding surfactant administration to the above explanatory variables. We had to deal with the hierarchical structure of the data consisting of infants in neonatal intensive care unit (NICU) and NICU in countries, leading to correlations within data. These correlations are contrary to the requirement of independence and may produce what is called extra-binomial variation: the variance of the dependent variable (here neonatal mortality and BPD) will be greater than expected under the assumption of a binomial distribution. This may result in underestimation of the standard errors and overestimation of the chi-square statistics. To correct for this problem, we divided all the individual chi-squares and standard errors by the ratio of the Pearson's goodness-of-fit chi-square to its degrees of freedom, leaving the coefficient estimates unchanged.[7,8]

We checked model fit by the '*c*-statistic'.[9] Since we were dealing with non-nested models (these are models in which no model is a subset of one of the other models), we carried out a model selection using the Bayesian Information Criterion (BIC).[10] BIC is a function of the probability of a model, the number of parameters and the number of observations. It ranks the models studied according to their score, with the lower the BIC score, the better the fit.

To assess the biases that might arise from missing data, we carried out bivariate (cross-tabulation) and multivariate (logistic regression) sensitivity analyses by creating a category for missing values for Apgar scores at 1 and 5 min and antenatal steroids and compared their effect with that of non-missing values on in-hospital mortality and BPD.

To illustrate the benefits of bringing together data from different countries, we conducted a power analysis. We calculated how many years would be needed for each country to identify a statistically significant difference in mortality following a hypothetical intervention. To improve intelligibility, we reduced the 3-year period of observations to average yearly number of admissions. We provide details of the calculations in Appendix 2.

Participation in the study was agreed on according to each country's national regulations. Agreements were network based or unit based.

RESULTS

We identified 39,529 infants in the eNewborn database over the 3-year period 2014–2016, born at or below a GA of 31 weeks and 6 days or ≤1500 g birth weight. Mortality and patient characteristics are shown in Table 1. The early neonatal, neonatal and in-hospital mortality rates were 3.90% (95% confidence interval (CI) 3.71, 4.09), 6.00% (95% CI 5.77, 6.24) and 7.57% (95% CI 7.31, 7.83), respectively. Of the 2373 babies who died in the neonatal period, approximately two-thirds were in the first postnatal week. Birth defects occurred in 7.29% ($n = 173$), which represents 0.43% of the neonatal deaths among which 0.18% ($n = 73$) were related to a major congenital or chromosomal anomaly. This is a negligible contribution, and therefore we did not include congenital anomalies in the multivariate analysis.

We show early neonatal, neonatal and in-hospital mortality rates and 95% CIs by GA for boys and girls combined in Fig. 1. The decline in mortality with increasing GA is exponential up to 26 weeks and stabilises afterwards.

Neonatal mortality by sex, birth weight and GA are shown in Fig. 2. To avoid the undue effect of superimposition of cases, we plotted a random sample, defined as equal to the number of deceased newborns, of boys and girls surviving the neonatal period in the upper part of the graphs. In the lower part, we plotted the corresponding graphs for deceased boys and girls. For ease of interpretation, we added the 3rd, 10th, 90th and 97th Fenton centiles. The figure shows greater representation of deceased babies at the lower GAs and in the growth-restricted categories.

Table 2 describes the correlation between the three categories of delivery room management (none, basic and advanced) and Apgar score. In the smallest GA groups (22–24 weeks), we observed very weak (<0.20) correlations between Apgar scores at both 1 and 5 min and delivery room care. The correlation coefficient between Apgar score and delivery room care increased with increasing GA from 0.13 at 22–24 weeks to 0.50 >30 weeks at 1 min and from 0.09 to 0.30 at 5 min. There were strong correlations (0.60) between both Apgar scores in the most immature GA groups decreasing progressively to a moderate correlation of 0.44 in the GA group ≥30 weeks.

For babies <25 weeks GA, 95% received advanced delivery room care if the 1 min Apgar score was between 0 and 3, 92% when the 1 min Apgar was 4–6 and 82% when the 1-min Apgar was 7–10. For GAs between 25–27 and 28–31 weeks, these

Table 1. (a) Main endpoints of the eNewborn database (2014–2017); (b) characteristics of survivors to discharge and non-survivors.

	Survivors to discharge		Died		Total
	N	%	*N*	%	
(a) Endpoints					
Early neonatal mortality	37,988	96.10	1541	3.90	39,529
Neonatal mortality	37,156	94.00	2373	6.00	39,529
In-hospital mortality	36,538	92.43	2991	7.57	39,529
Oxygen at 36 weeks					
No	26,978	77.73	695	23.31	27,673
Yes	7726	22.26	184	6.17	
Not applicable	3	0.01	2102	70.51	2105
Missing	1831		10		1835
(b) Characteristics					
Gestational age					
5th percentile	25		23		
Lower quartile	28		24		
Mean	29		26		
Median	30		25		
Upper quartile	31		28		
95th percentile	32		31		
Birth weight (g)					
5th percentile	668		480		
Lower quartile	985		610		
Mean	1241		848		
Median	1260		750		
Upper quartile	1470		990		
95th percentile	1800		1495		
Gestational age					
22	11	0.03	31	1.04	42
23	341	0.93	395	13.21	736
24	1132	3.10	621	20.76	1753
25	1689	4.62	497	16.62	2186
26	2281	6.24	384	12.84	2665
27	3021	8.27	249	8.32	3270
28	3911	10.70	252	8.43	4163
29	4721	12.92	172	5.75	4893
30	6153	16.84	142	4.75	6295
31	7924	21.69	140	4.68	8064
32	5352	14.65	108	3.61	5460
Missing	2		0		2
Birth weight class, g					
250–499	191	0,52	206	6.89	397
500–749	3049	8,35	1262	42.19	4311
750–999	6314	17.29	788	26.35	7102
1000–1249	8152	22.32	343	11.47	8495
1250–1499	11,348	31.07	243	8.12	11,591
1500+	7471	20.45	149	4.98	7620
Missing	13		0		13
Gender					
Female	17,441	47.77	1267	42.42	18,708
Male	19,070	52.23	1720	57.58	20,790
Missing	27		4		31
Multiple birth					
No	25,595	70.06	2178	72.82	27,773
Yes	10,937	29.94	813	27.18	11,750
Missing	6		0		6
Inborn/outborn					
Inborn	33,774	92.46	2639	88.32	36,413
Outborn	2756	7.54	349	11.68	3105
Missing	8		3		11
Dysmaturity[a]					
ESGA	2907	7.96	272	9.11	3179
SGA	4042	11.07	285	9.54	4327
AGA	29,560	80.97	2430	81.35	31,990
Missing	29		4		33
Apgar 1 min					
Apgar1: 0–3	5087	14.79	1224	44.74	6311
Apgar1: 4–6	10,778	31.33	1005	36.73	11,783
Apgar1: 7–10	18,538	53.88	507	18.53	19,045
Missing	2135		255		2390
Apgar 5 min					
Apgar5: 0–3	857	2.50	483	17.71	1340
Apgar5: 4–6	4607	13.43	904	33.14	5511
Apgar5: 7–10	28,849	84.08	1341	49.16	30,190
Missing	2225		263		2488
Prenatal steroids					
Complete	24,992	69.96	1657	57.06	26,649
Incomplete	7470	20.91	696	23.97	8166
None	3261	9.13	551	18.97	3812
Missing	815		87		902
Delivery room care[b]					
Advanced resuscitation	13,111	35.90	2405	80.52	15,516
Basic resuscitation	16,491	45.15	412	13.79	16,903
None	6923	18.95	170	5.69	7093
Missing	13		4		17
Surfactant					
No	18,788	51.76	367	12.47	19,155
Yes	17,509	48.24	2575	87.53	20,084
Missing	241		49		290

[a]Extremely small for gestational age (ESGA) and small for gestational age (SGA): defined according to Fenton Growth charts.
[b]Delivery room care: basic resuscitation: oxygen or positive pressure bag and mask ventilation; advanced resuscitation: intubation, cardiac compression, adrenaline/epinephrine.

percentages were 90%, 80% and 56% and 69%, 40% and 14%, respectively.

Table 3 shows a significant ($p < 0.001$) discrepancy between the observed and expected values obtained by an independent model for both antenatal steroids and 5 min Apgar score. There was a significant improvement in Apgar score between 1 and 5 min (Bowker's test for symmetry: $p < 0.0001$). Overall, 59.6% of the 36,877 newborns had the same Apgar score at 1 and 5 min, 39.3% had an improved score and 1.1% a deteriorated score (Table 2). Of the 36,877 babies, 6251 (17.0%) had a 1-min Apgar score between 0 and 3. Of these, by 5 min, 19.8% had a similar

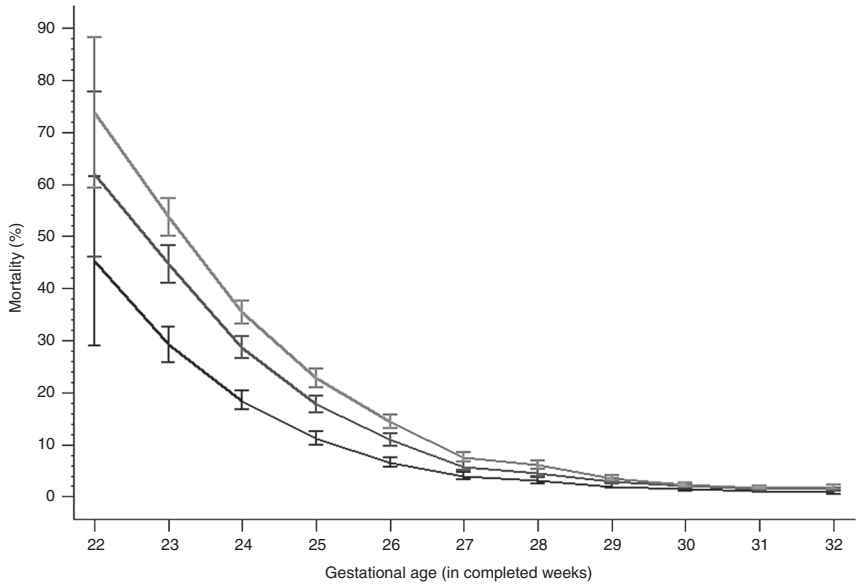

Fig. 1 Early neonatal (black), neonatal (blue), and in-hospital mortality (red) rates; mean and 95% confidence intervals, by gestational age (in completed weeks), for boys and girls combined.

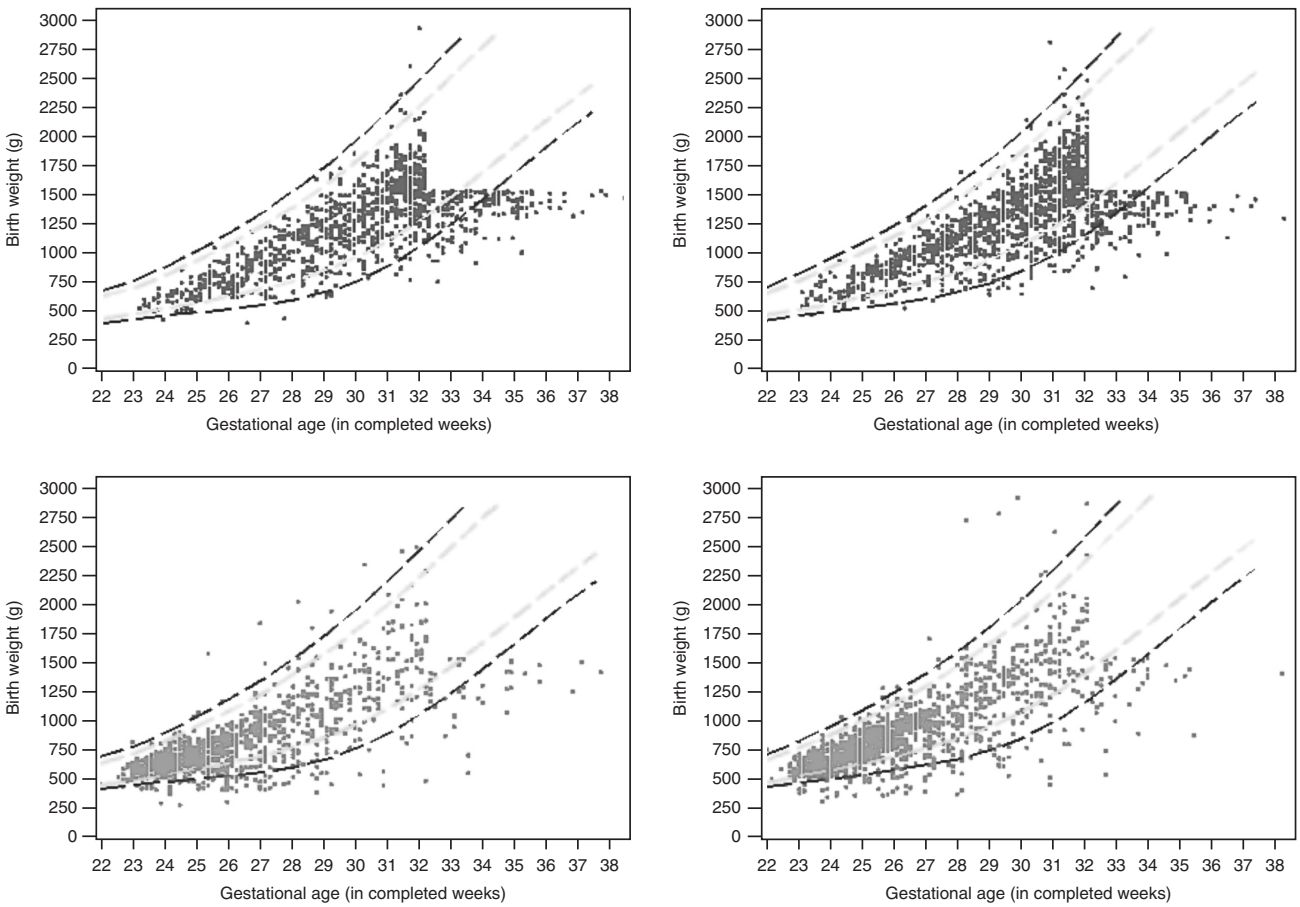

Fig. 2 Neonatal mortality by sex, birth weight, and gestational age. Neonatal survivors and deaths. Upper panel left: random sample of 1021 survivors (girls); Upper panel right: random sample of 1346 survivors (boys). Lower panel left: 1021 deaths (girls); Lower panel right: 1346 deaths (boys). Dashed lines from bottom to top 3rd, 10th, 90th, and 97th Fenton centile.

Apgar score, 47.7% had a score of 4–6 and 32.5% a score of 7–10. Of the newborns with a 1-min Apgar score of 4–6, by 5 min 80.9% had an improved and 0.6% a deteriorated score. Of those with a 1-min Apgar score of 7–10, 1.9% had a worse score at 5 min.

Increasing compliance with administration of antenatal steroids was associated with higher Apgar scores ($p < 0.001$).

The logistic regression modelling showed increased neonatal mortality with advanced delivery room resuscitation, Apgar scores

Table 2. Delivery room care (by category) by Apgar 1- and 5-min scores (by category) and gestational age (in completed weeks and by category), expressed in percentages and Spearman's rank correlation coefficients.

GA, weeks	DRC	Apgar 1-min score			Apgar 5-min score			*N*	Correlations		
		0–3 %	4–6 %	7–10 %	0–3 %	4–6 %	7–10 %		$rs_{DRC-AP1}$	$rs_{DRC-AP5}$	$rs_{AP1-AP5}$
22–24	Adv	94.7	91.7	82.1	92.8	95.5	88.7	2089	0.13	0.09	0.60
	Bas	3.3	7.8	13.4	2.5	3.8	9.6	148	(0.09; 0.17)	(0.05; 0.13)	(0.57; 0.62)
	Non	2.0	0.5	4.6	4.7	0.7	1.7	40			
	Col Tot	1029	941	307	319	838	1120	2277			
25–27	Adv	89.8	79.4	56.0	94.0	89.9	68.4	5638	0.31	0.24	0.58
	Bas	9.8	19.3	38.1	4.8	9.5	28.4	1680	(0.28; 0.33)	(0.22; 0.26)	(0.56; 0.59)
	Non	0.4	1.3	5.9	1.3	0.6	3.2	185			
		2084	3132	2287	480	1786	5237	7503			
28–30	Adv	68.5	40.1	13.9	90.5	67.2	22.0	6316	0.46	0.35	0.48
	Bas	30.1	56.9	58.8	7.0	31.2	59.0	11,977	(0.45; 0.48)	(0.34; 0.37)	(0.47; 0.49)
	Non	1.4	3.0	27.2	2.5	1.6	19.0	3645			
		2791	6629	12,518	473	2564	18,901	21,938			
>30	Adv	45.9	14.3	2.5	73.6	41.0	5.0	395	0.50	0.30	0.44
	Bas	51.7	79.5	42.2	22.6	55.8	50.0	2574	(0.48; 0.52)	(0.27; 0.32)	(0.42; 0.46)
	Non	2.33	6.21	55.37	3.8	3.2	45.0	2175			
		344	998	3802	53	283	4808	5144			

GA gestational age (in completed weeks), *DRC* delivery room care (*Non* no resuscitation, *Bas* basic resuscitation, *Adv* advanced resuscitation), *%* column percentages by GA class, *N* number of infants by GA class, column tot number of infants by Apgar score class, $rs_{DRC-AP1}$ Spearman's rank correlation coefficient between DRC and Apgar 1 min score by GA class, $rs_{DRC-AP5}$ Spearman's rank correlation coefficient between DRC and Apgar 5 min score by GA class, $rs_{AP1-AP5}$ Spearman's rank correlation coefficient between Apgar 1 min score and Apgar 5 min score by GA class, 95% confidence interval of the Spearman's rank correlation coefficients.

Table 3. Apgar score at 1 vs 5 min and administration of antenatal steroids.

Apgar 1-min score	Apgar 5-min score, min							Course of antenatal steroids						
	0–3		4–6		7–10			None		Incomplete		Complete		
	Obs	Exp	Obs	Exp	Obs	Exp	Total	Obs	Exp	Obs	Exp	Obs	Exp	Total
0–3	1235	224.77	2984	927.73	2032	5098.5	6251	905	578.82	1617	1320.3	3647	4269.9	6169
4–6	68	420.7	2163	1736.4	9469	9542.9	11,700	1028	1081.5	2610	2467.1	7889	7978.4	11,527
7–10	23	680.53	326	2808.9	18,577	15,437	18,926	1479	1751.6	3556	3995.6	13,634	12,922	18,669
Total	1326		5473		30,078		36,877	3412		7783		25,170		36,365

Obs observed values, *Exp* expected values (obtained by fitting a model of no association between 1- and 5-min Apgar scores and between 1-min Apgar score and antenatal steroids).

of 0–3 and 4–6, no improvement of very low Apgar scores, decreasing GA, ESGA and SGA status, boys, multiple births and no antenatal steroids (Table 4). Babies with an incomplete course of antenatal steroids also fared worse than those with a complete course. The fit of the models was very good, all had a *c*-statistic between 0.84 and 0.86. According to the BIC, the ranking of the models was as follows: (1) delivery room care, (2) Apgar score at 5 min, (3) Apgar score at 1 min, and (4) evolution of the Apgar score.

In the BPD logistic regression modelling, we observed an adverse association with advanced delivery room resuscitation, Apgar scores of 0–3 and 4–6, decreasing GA, ESGA and SGA status, boys, multiple births, surfactant administration and a complete antenatal steroid course (Table 4). The fit of the models was very good; all had a *c*-statistic between 0.84 and 0.85. According the BIC the ranking of the models was as follows: (1) Apgar score at 5 min, (2) delivery room care, (3) Agar score at 1 min, and (4) evolution of the Apgar score.

The association between missing 1- and 5-min Apgar scores and neonatal mortality was very similar to that of the non-missing scores in both bivariate and multivariable analyses. Similarly, the effect of missing antenatal steroids was close to the 'incomplete antenatal steroid course' category. In the bivariate analysis, infants with a missing 1-min Apgar score had a 3.5% lower risk of BPD than the lowest 1-min Apgar score category, whereas in the multivariable analysis BPD risk was 7% higher. In the same analyses, with 'missing antenatal steroids' compared to non-missing antenatal steroids, we observed about 5% higher risk in the former in both the bivariate and multivariable analyses.

In Table 5, we display the number of years needed for each country or network to achieve 80% power to identify a statistically

Table 4. Neonatal mortality and bronchopulmonary dysplasia, expressed as odds ratios (OR) and 95% confidence intervals (95% CI), as a function of delivery room care, 1-min Apgar score, 5-min Apgar 5 score or evolution of the Apgar score between 1 and 5 min, adjusted for gestational age, birth weight, antenatal steroids, multiple birth, sex and surfactant administration (BPD only).

		Model delivery room care			Model 1-min Apgar score			Model 5-min Apgar score			Evolution Apgar score		
		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Covariate: neonatal mortality		(*N* = 38,582)			(*N* = 36,334)			(*N* = 36,245)			(*N* = 36,084)		
Delivery room care	Adv Res vs None	2.52	1.98	3.22	–	–	–	–	–	–	–	–	–
	Basic vs None	0.98	0.76	1.27	–	–	–	–	–	–	–	–	–
Apgar score	0–3 vs 7–10	–	–	–	3.41	2.90	4.00	5.17	4.31	6.20	–	–	–
	4–6 vs 7–10	–	–	–	1.86	1.59	2.18	2.17	1.89	2.47	–	–	–
Evolution Apgar score	1151 vs 1353	–	–	–	–	–	–	–	–	–	7.69	6.29	9.40
	1152 vs 1353	–	–	–	–	–	–	–	–	–	3.06	2.55	3.66
	1153 vs 1353	–	–	–	–	–	–	–	–	–	1.93	1.53	2.44
	1251 vs 1353	–	–	–	–	–	–	–	–	–	2.80	1.17	6.71
	1252 vs 1353	–	–	–	–	–	–	–	–	–	3.05	2.49	3.73
	1253 vs 1353	–	–	–	–	–	–	–	–	–	1.62	1.38	1.91
	1351 vs 1353[a]	–	–	–	–	–	–	–	–	–	<0.001	<0.001	>999
	1352 vs 1353	–	–	–	–	–	–	–	–	–	1.54	0.77	3.08
GA	22 vs 31	50.59	21.62	118.36	43.13	17.35	107.23	45.02	17.36	116.74	38.77	16.01	93.87
	23 vs 31	28.02	20.71	37.91	35.11	25.75	47.86	36.74	26.68	50.60	31.57	23.36	42.67
	24 vs 31	16.12	12.25	21.20	20.96	15.90	27.64	22.69	17.09	30.14	19.68	15.06	25.72
	25 vs 31	9.00	6.83	11.86	11.71	8.86	15.47	12.85	9.66	17.10	11.25	8.60	14.72
	26 vs 31	5.24	3.96	6.95	7.10	5.34	9.43	7.76	5.80	10.40	6.85	5.20	9.01
	27 vs 31	2.75	2.04	3.69	3.52	2.61	4.76	3.84	2.81	5.24	3.47	2.60	4.65
	28 vs 31	2.31	1.72	3.10	2.93	2.17	3.96	3.15	2.32	4.29	2.96	2.22	3.95
	29 vs 31	1.68	1.24	2.28	2.04	1.49	2.80	2.21	1.60	3.06	2.10	1.56	2.85
	30 vs 31	1.38	1.02	1.88	1.46	1.06	2.01	1.50	1.08	2.09	1.48	1.08	2.01
	32 vs 31	0.56	0.38	0.82	0.60	0.40	0.88	0.56	0.37	0.84	0.61	0.42	0.89
Birth weight	ESGA vs AGA	3.33	2.63	4.22	3.24	2.54	4.14	3.46	2.68	4.46	3.32	2.63	4.20
	SGA vs AGA	1.48	1.21	1.81	1.44	1.17	1.77	1.48	1.19	1.83	1.44	1.18	1.75
Antenatal steroids	None vs incomplete	2.22	1.88	2.63	2.22	1.86	2.66	2.09	1.73	2.51	2.10	1.76	2.50
	None vs complete	2.76	2.38	3.19	2.56	2.19	3.00	2.48	2.10	2.92	2.44	2.09	2.84
	Incomplete vs complete	1.24	1.09	1.41	1.15	1.01	1.32	1.19	1.03	1.37	1.16	1.02	1.32
Multiple birth	Yes vs no	1.14	1.01	1.28	1.22	1.08	1.38	1.24	1.09	1.41	1.24	1.10	1.40
Sex	Boys vs girls	1.20	1.07	1.33	1.20	1.07	1.34	1.18	1.05	1.33	1.18	1.05	1.31
Model fit	*c*-statistic	0.840		0.847	0.851		0.856						
Model selection	BIC	2237		2501	2402		3556						
Covariate: bronchopulmonary dysplasia		(*N* = 33,809)			(*N* = 31,956)			(*N* = 31,877)			(*N* = 31,744)		
Delivery room care	Adv Res vs None	1.66	1.43	1.91	–	–	–	–	–	–	–	–	–
	Basic vs None	0.94	0.82	1.08	–	–	–	–	–	–	–	–	–
Apgar score	0–3 vs 7–10	–	–	–	1.50	1.35	1.66	1.43	1.16	1.76	–	–	–
	4–6 vs 7–10	–	–	–	1.37	1.26	1.49	1.24	1.12	1.37	–	–	–
Evolution Apgar score	1151 vs 1353	–	–	–	–	–	–	–	–	–	1.74	1.41	2.16
	1152 vs 1353	–	–	–	–	–	–	–	–	–	1.55	1.36	1.77
	1153 vs 1353	–	–	–	–	–	–	–	–	–	1.34	1.15	1.55
	1251 vs 1353	–	–	–	–	–	–	–	–	–	1.32	0.64	2.71
	1252 vs 1353	–	–	–	–	–	–	–	–	–	1.42	1.23	1.65
	1253 vs 1353	–	–	–	–	–	–	–	–	–	1.37	1.25	1.49
	1351 vs 1353	–	–	–	–	–	–	–	–	–	1.21	0.32	4.52
	1352 vs 1353	–	–	–	–	–	–	–	–	–	0.90	0.61	1.34
GA	22 vs 31	119.86	9.59	>999	112.07	10.06	>999	118.37	9.90	>999	112.37	11.07	>999
	23 vs 31	58.61	37.89	90.66	59.88	39.13	91.63	60.44	39.17	93.25	57.42	38.08	86.58
	24 vs 31	38.02	30.04	48.11	38.78	30.90	48.67	41.25	32.67	52.08	38.28	30.73	47.68
	25 vs 31	18.91	15.64	22.86	20.27	16.87	24.36	21.51	17.81	25.98	20.16	16.88	24.08

Table 4 continued

		Model delivery room care			Model 1-min Apgar score			Model 5-min Apgar score			Evolution Apgar score		
		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
	26 vs 31	11.46	9.64	13.62	12.04	10.18	14.24	12.44	10.47	14.78	11.93	10.14	14.03
	27 vs 31	7.63	6.49	8.98	7.72	6.59	9.05	7.94	6.75	9.34	7.67	6.58	8.94
	28 vs 31	4.58	3.91	5.37	4.75	4.07	5.54	4.84	4.13	5.67	4.75	4.10	5.52
	29 vs 31	2.79	2.38	3.27	2.81	2.40	3.28	2.87	2.44	3.36	2.82	2.43	3.28
	30 vs 31	1.77	1.51	2.08	1.73	1.48	2.03	1.74	1.47	2.05	1.72	1.47	2.00
	32 vs 31	0.39	0.31	0.49	0.40	0.32	0.50	0.38	0.30	0.48	0.39	0.32	0.49
Birth weight	ESGA vs AGA	4.80	3.91	5.89	5.06	4.14	6.19	5.17	4.20	6.36	5.03	4.15	6.12
	SGA vs AGA	3.13	2.74	3.57	3.11	2.74	3.53	3.14	2.75	3.58	3.11	2.75	3.52
Antenatal steroids	None vs incomplete	1.22	0.09	1.42	1.16	0.09	1.35	1.16	0.99	1.36	1.14	0.09	1.33
	None vs complete	0.83	0.72	0.95	0.77	0.67	0.88	0.76	0.66	0.88	0.75	0.05	0.86
	Incomplete vs complete	0.68	0.62	0.74	0.66	0.60	0.72	0.66	0.60	0.73	0.66	0.03	0.72
Multiple birth	Yes vs No	1.11	1.02	1.20	1.10	1.02	1.20	1.10	1.01	1.20	1.10	1.02	1.20
Sex	Boys vs girls	1.35	1.26	1.46	1.35	1.25	1.45	0.36	0.32	0.39	0.37	0.34	0.41
Surfactant	No vs yes	0.48	0.43	0.53	0.37	0.34	0.41	1.35	1.25	1.46	1.35	1.26	1.46
Model fit	*c*-statistic	0.848		0.849	0.851		0.848						
Model selection	BIC	3674		3769	3208		5048						

Delivery room care (*Adv Res* Advanced resuscitation, *Basic* Basic resuscitation, *None* No resuscitation); 1- and 5-min Apgar score categories: 0–3, 4–6, 7–10; Evolution Apgar score '1151': Apgar score 1 min: 0–3 and Apgar score 5 min: 0–3; Evolution Apgar score '1152': Apgar score 1 min: 0–3 and Apgar score 5 min: 4–6; Evolution Apgar score '1153': Apgar score 1 min: 0–3 and Apgar score 5 min: 7–10; Evolution Apgar score '1251': Apgar score 1 min: 4–6 and Apgar score 5 min: 0–3; Evolution Apgar score '1252': Apgar score 1 min: 4–6 and Apgar score 5 min: 4–6; Evolution Apgar score '1253': Apgar score 1 min: 4–6 and Apgar score 5 min: 7–10; Evolution Apgar score '1351': Apgar score 1 min: 7–10 and Apgar score 5 min: 0–3; Evolution Apgar score '1352': Apgar score 1 min: 7–10 and Apgar score 5 min: 4–6; Evolution Apgar score '1353': Apgar score 1 min: 7–10 and Apgar score 5 min: 7–10; gestational age: gestational age in completed weeks; antenatal steroids: any administration of antenatal steroids.
ESGA extremely small for gestational age, *SGA* small for gestational age, *AGA* appropriate for gestational age, *OR* odds ratio, *95% CI* 95% confidence interval, *BIC* Bayesian Information Criterion.
[a]Apgar '1351' vs '1353': in this situation, we observed 0 deaths out of 23 patients in this category (OR not estimable).

Table 5. Number of years needed by a country, given the average yearly number of admissions of babies born at 23, 24 and 25 weeks' gestation and all three gestational age bands combined, to achieve 80% power to detect a statistically significant change in neonatal mortality and BPD rates in response to a hypothetical intervention, aiming at a 5% change in these rates.

		Rate observed in eNewborn	Hypothetical % change in rate	Number of babies needed to achieve 80% power		Belgium	Czech Republic	Portugal	Switzerland	UK	eNewborn
NMR	GA				AYNA	5	21	9	10	194	245
	23	44.7	5%	1571	NYNC	294	76	168	152	8	6
					AYNA	46	39	37	41	391	584
	24	28.6	5%	1250	NYNC	27	32	33	31	3	2
					AYNA	76	59	51	55	453	729
	25	17.7	5%	848	NYNC	11	14	17	15	2	1
					AYNA	127	119	97	106	1038	1558
	23–25	26.0	5%	1169	NYNC	9	10	12	11	1	1
BPD					AYNA	2	5	1	4	90	104
	23	87.5	5%	840	NYNC	420	157	840	210	9	8
					AYNA	24	25	14	23	247	345
	24	80.5	5%	1116	NYNC	46	45	82	48	5	3
					AYNA	54	41	29	34	330	510
	25	66.7	5%	1482	NYNC	28	36	51	44	4	3
					AYNA	80	72	61	61	667	960
	23–25	73.9	5%	1321	NYNC	17	18	22	22	2	1

NMR neonatal mortality rate, *BPD* bronchopulmonary dysplasia, *GA* gestational age (in completed weeks), *AYNA* average yearly number of admissions, *NYNC* number of years needed by country to achieve 80% power.

significant change in neonatal mortality and BPD in 23, 24 and 25 weeks' GA infants. The data are presented for countries with complete data, using their 'rates' as present in the database and assuming these countries have similar therapeutic approaches and outcomes in terms of neonatal mortality and BPD.

DISCUSSION

In this first analysis of the eNewborn database, we provide baseline figures for mortality and BPD for almost 40,000 very preterm/very low birth weight babies across Europe. We show that in-hospital mortality mirrors survival rates reported elsewhere[11,12] with the 50% GA-specific mortality rate situated at 23–24 weeks, also in keeping with other studies.[13] However, the Epice Research Group study reported an in-hospital mortality of 13.6% compared to that of our cohort, namely 7.6 %. This might be partly due to the inclusion of all babies <32 weeks or <1500 g in eNewborn with more growth-restricted mature babies increasing the survival rate.

We showed a significant increase in Apgar scores between 1 and 5 min and an association between increasing compliance with antenatal steroid administration and increased 1-min Apgar score.[14] We found that, of babies with a 1-min Apgar score between 0 and 3, almost 20% had no improvement by 5 min. We further observed (1) a higher mortality for Apgar scores of 0–3 and 4–6 at 1 min and for Apgar score 0–3 at 5 min and (2) lowered mortality with improved Apgar scores at 5 min, indicating the importance of recovery in the very few first minutes of life.

We also found for babies with a 1-min Apgar score of 7–10, indicating good condition at birth, that advanced delivery room care was reported for >80% of babies at <25 weeks' GA and over half at 25–27 weeks but was associated with high mortality and BPD. We identified as anticipated a predominant association between decreasing GA and adverse outcomes and significant associations with low Apgar scores, growth restriction, male sex and multiple birth. The odds of death were reduced across all GAs in infants who received both a complete or incomplete course of antenatal steroids. However, improved survival was accompanied by a higher risk of BPD.

The strengths of our study are the large number of infants, with <10% missing values,[15] and the number of countries contributing complete or near complete neonatal unit admission data (Appendix 1). Europe has small and large countries and therefore their individual data contributions are inevitably non-homogenous. Differences in morbidity and mortality have been largely described between neonatal units and hospitals[16–20] but less often between and within countries. We included several adjustments (GA, Apgar scores, AGA, gender, multiplets, prenatal steroids) that impact on mortality in our logistic regressions. The *c*-statistics, reflecting the fit of the models, are very good (all between 0.84 and 0.86) and therefore not including country as a covariate into the analysis seems not to have been a major drawback. The selection of 'Model Delivery Room Care' as the best performing model in the context of neonatal mortality is due to the higher number of observations, its log-likelihood of −4993.7 being smaller than that be considered of −4297.7 of 'Model 5 min Apgar score'. In the context of BPD, 'Model 5 min Apgar score' performed best (see Appendix 3: model fit and model selection). Although 'Evolution Apgar score' is an appealing model, it remains a second-choice model due to a lesser likelihood and an increased number of parameters (combinations).

Furthermore, we limited ourselves in this exploratory phase to main effects models (models without interactions) as these are easier to understand than models with interactions. The fit of our models was such that the effect of the interactions was minimal. However, if we want to assess prediction, we must take interactions into account; for example, Fig. 2 clearly shows that there is an interaction between GA and birth weight category on neonatal mortality. Identifying optimal weightings and validating them needs sophisticated analyses and large data sets, hence will be possible in the future when the network has grown.

We also show that bias due to missing data was marginal for BPD and absent for Apgar scores. Study weaknesses are that we had no means to quality assure or cross-validate data submitted directly by individual neonatal units, incomplete population coverage and inconsistent definitions of key outcome measures, such as BPD.[21] Further we have no information on socioeconomic status and other maternal details nor risk variables such as the Clinical Risk Index of Babies score.

Despite limitations, we feel some broad observations are possible. As anticipated, the most immature babies had lower Apgar scores than babies of greater maturity. Reassuringly, we identified a positive correlation between antenatal steroid exposure and 1-min Apgar score. In the most immature groups, we identified both a poor correlation between 1- and 5-min Apgar scores and delivery room care. This suggests that, across the countries represented, neonatal teams may not be necessarily intervening with advanced resuscitation attempts in the most immature infants, reflecting current thinking in relation to the care of infants at the margins of viability. The high reported rate of advanced delivery room care in babies in good condition at birth, particularly in those of greater immaturity, suggests persisting resistance to adopting a gentler, less intrusive approach to immediate newborn care, with intervention only when clearly warranted.[22] More research is needed to define best strategies and types of intervention for better outcomes and can only be achieved practically through international collaboration. In Sweden, wide regional variations are observed in mortality and in management. Proactive care did not increase the risk of neurodevelopment impairment at 2.5 years.[23] But the definition of pro-active care can be different in different settings.

There is strong evidence that antenatal steroids reduce the risk of BPD and our finding of greater odds of BPD following a complete course of antenatal steroids is likely to be a consequence of survival bias. However, the evidence base for antenatal steroids in women at risk of preterm birth has changed following a trial in low- and middle-income settings that identified harms, including greater risk of neonatal sepsis, itself a risk factor for death and BPD.[24] Further, a reappraisal of the Cochrane review evidence has indicated that generalisability across all settings should not be assumed. Though the countries contributing to eNewborn are all high income, they nonetheless are likely to encompass considerable heterogeneity in respect of patient characteristics, no less in care practices.[25,26] In addition, many practices have changed since the randomised trials of antenatal steroids were performed, and it is not inconceivable that the balance of benefits to risks may also have altered. Current recommendations for delivery room interventions have changed over time to encourage less invasive techniques.[27] Large population data sets such as eNewborn offer potential to re-evaluate treatments over time.

The eNewborn database is in its infancy and has as yet limited coverage. The Vermont Oxford Network started in 1988 and is far larger with a wide range of outputs but also suffers from incomplete population coverage.[28] The use of the eNewborn database has thus far been limited to benchmarking. However, a unique aspect is the interactive navigation that has been described elsewhere.[4] Data are provided on a collaborative basis and no financial contribution is required by participants. The sustainability of the network is based on external funding from grants, donations and commissions.

The eNewborn platform benefits from flexible data capture and can accommodate direct online recording as well as receive extracts from established databases with quality-assured data, such as the UK National Neonatal Research Database.[4,29] Clinicians

are rightly and increasingly required to audit care practices against accepted standards, conduct comparative evaluation of outcomes nationally and internationally and undertake quality improvement programmes. The UK Royal College of Paediatrics and Child Health has run a National Neonatal Audit Programme since 2007, and because data for the audit are obtained from the National Neonatal Research Database, clinical teams are not faced with the burdens of added data collection.[29] More widespread country-wide participation could drive rigorous pan-European audit especially if overseen by a cross-national authority such as the newly established European Board of Neonatology as part of the European Society of Paediatric Research (https://www.espr.eu/). The introduction of neonatal care standards by the European Foundation for the Care of the Newborn Infant (https://www.efcni.org/) also now provides a potential focus for audit (https://newborn-health-standards.org/). International collaboration can also drive improvements in care by, for example, identifying variation, providing benchmarks and identifying potential areas for improvement such as delivery room resuscitation, as indicated by our findings.

Many newborn interventions have an inadequate evidence base, providing a clear impetus for comparative effectiveness studies. Most neonatal medications continue to be used off-license or off-label, because they have not been evaluated in relevant patient groups. These chronic issues call for sustained emphasis on clinical and translational research. However, we show that it would take a country such as Belgium 9 years and 17 years, respectively, to have a sufficient number of eligible babies to achieve 80% power to detect a statistical significant change in neonatal mortality and BPD following a hypothetical intervention in babies of 23–25 weeks' GA, in contrast to 1 year for the eNewborn network as a whole. International collaboration offers the only real hope for conducting studies aiming to identify impacts of interventions that are unlikely to have arisen by chance.

In summary, we provide illustrative data describing potential uses of the eNewborn database. Neonatal critical care is a high-cost service that is justified both by the moral imperative to provide quality care for sick newborn infants and because of its life-long impact. The eNewborn platform offers opportunity for high-quality data capture across neonatal services in Europe and the means to drive audit, quality improvement and research.

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D.H.: building of the eNewborn network and data collection and drafted the article. N.M.: main partner and contributor in eNewborn network and database, director National Neonatal Research Database NNRD (UK), and participated actively in the writing process. O.D.S.: participated actively in analysis of the results and their relevance. R.A.: effectuated the data management, mapping and contacts with participating units. C.N.: IT responsible and conceptor of eNewborn software platform. M.T.: gave important incentives to neonatal units to participate in eNewborn and contributed in writing the article. K.C.: shared our vision with her experience of databases and supported the development of the network. W.A.: performed all the statistical analyses and discussed the pertinence of the results.

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APPENDICES

1. Distribution of the 39,529 patients per national network and the individual units.

	N	%
Belgium	3,835	9.7
Czech Republic	2,979	7.5
Portugal	2,965	7.5
Switzerland	2,677	6.8
United Kingdom	25,134	63.6
Individual units	1,945	4.9

2. In order to take sampling fluctuations into account, we adopted a cautious approach wherein we sought to detect a significant difference between true mortality rates π1 and π2, estimated respectively by the 'actual' and the 'future' mortality rate in the eNewborn database. We tested the null hypothesis that each mortality rate was equal to the pooled mortality rate π. To compute the sample size (Nbr in the table) needed to achieve 80% power to detect a statistically significant change in neonatal mortality and BPD rates in response to a hypothetical intervention, aiming at a 5% change in these rates, we used the formula:[30]

$$N > \left[\left[\left(z_{2\alpha}\mathrm{sqrt}\left(2\pi(1-\pi)+z_{2\beta}\mathrm{sqrt}(\pi1(1-\pi1)+\pi2(1-\pi2))\right)\right)\right]/(2/d)\right]^2$$

with Fleiss correction[31] of 2/(|π1-π2|),

where *N* is the number of observations needed, *π* is the pooled rate of *π1*, the actual rate, and *π2*, the decreased rate, *d* is the difference between actual and future rates, $z_{2\alpha} = 1.96$ and $z_{2b} = 0.8418$.

3. Model fit and model selection.

	Neonatal mortality			
	Model delivery room care (*N* = 38.582)	Model 1 min apgar score (*N* = 36.334)	Model 5 min apgar score (*N* = 36.245)	Evolution apgar score (*N* = 36.084)
C Statistic	0.840	0.847	0.851	0.856
BIC	2237	2501	2402	3556
Loglikelihood	−4993.7	−4596.3	−4297.8	−4939.1
Number of parameters	25	25	25	31
	BPD			
	Model delivery room care (*N* = 33.809)	Model 1 min apgar score (*N* = 31.956)	Model 5 min apgar score (*N* = 31.877)	Evolution apgar score (*N* = 31.744)
C Statistic	0.848	0.849	0.851	0.848
BIC	3674	3769	3208	5048
Loglikelihood	−8664.9	−9024	−8508.5	−9664.8
Number of parameters	27	27	27	33

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