REGULAR ARTICLE

ACTA PÆDIATRICA
NURTURING THE CHILD
WILEY

Birth outcomes between 22 and 26 weeks' gestation in national population-based cohorts from Sweden, England and France

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Funding information
This project was funded by the European Union's Horizon 2020 Research and Innovation Program (RECAP Preterm Project, grant no. 733280) (ASM, JZ, KK, ESD, SvB, SJ, VP, VB and PYA). ASM additionally received part funding from the Fondation pour la Recherche Médicale (reference SPF20160936356), and NM receives part funding from the Department of Health's NIHR Biomedical

Abstract

Aim: We investigated the timing of survival differences and effects on morbidity for foetuses alive at maternal admission to hospital delivered at 22 to 26 weeks' gestational age (GA).

Methods: Data from the EXPRESS (Sweden, 2004–07), EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts were harmonised. Survival, stratified by GA, was analysed to 112 days using Kaplan-Meier analyses and Cox regression adjusted for population and pregnancy characteristics; neonatal morbidities, survival to discharge and follow-up and outcomes at 2–3 years of age were compared.

Results: Among 769 EXPRESS, 2310 EPICure-2 and 1359 EPIPAGE-2 foetuses, 112-day survival was, respectively, 28.2%, 10.8% and 0.5% at 22–23 weeks' GA; 68.5%, 40.0% and 23.6% at 24 weeks; 80.5%, 64.8% and 56.9% at 25 weeks; and 86.6%,

77.1% and 74.4% at 26 weeks. Deaths were most marked in EPIPAGE-2 before 1 day at 22–23 and 24 weeks GA. At 25 weeks, survival varied before 28 days; differences at 26 weeks were minimal. Cox analyses were consistent with the Kaplan-Meier analyses. Variations in morbidities were not clearly associated with survival.

Conclusion: Differences in survival and morbidity outcomes for extremely preterm births are evident despite adjustment for background characteristics. No clear relationship was identified between early mortality and later patterns of morbidity.

KEYWORDS
epidemiology, extreme preterm birth, international comparisons, neonatal, perinatal, survival analysis

1 | BACKGROUND

Care and outcomes of extremely preterm birth, including ethical decisions, were recently identified by an international Delphi consensus panel including healthcare professionals, patient representatives and policy makers as a top priority theme for investigation.[1] Because of the high risk of long-term health consequences among survivors of birth before 27 weeks of gestation, most notably neurosensory impairment, understanding how care around birth and during initial hospitalisation can be improved to optimise survival without major morbidity is of major interest.

Survival of babies born at 22 to 26 completed weeks of gestational age (GA) varies widely both within and between countries; this variation has been primarily attributed to ethical decisions regarding the institution of active management around the time of birth.[2–4] However, variation could be due to methodological differences such as the choice of baseline population,[5] whether subject identification is by specialist centres or conducted geographically, or through

> **Key notes**
> - Survival for births at 22–26 weeks' gestation varies internationally, but little is known about the causes behind these differences.
> - Large differences in survival of extremely preterm births occur during labour and the first hours and days after birth, particularly at the lowest gestational ages, which are not explained by population baseline or maternal and foetal characteristics.
> - A major possible explanation for these differences is variation in societal choices between countries.

differential recording of live and stillbirths.[6] Differences in 28-day survival have been demonstrated in aggregated population level registries[7] but, given the challenges, few studies evaluate confounding

due to population factors concerning complications of pregnancy. Even less is known about relationships between obstetric and neonatal care and longer term impairments: It is feared that active management may result in a larger proportion of survivors with disability, but reports are contradictory, and high-quality comparative data are scarce. Detailed data are not available in population registries, and many neonatal registers only follow the infants until final discharge from hospital.[8] Questions, therefore, persist about how varying management strategies might affect longer term health of survivors.

In order to compare and contrast management and outcomes, we combined data from three prospectively collected, national population-based European cohort studies of extremely preterm births carried out in Sweden, England and France. The aim of this study was to analyse country-level differences using harmonised populations and variables, thus ensuring data consistency and enabling detailed investigation of outcomes at different time points. We compared survival patterns over time and sought to understand associations with population characteristics at discharge and follow-up in early childhood. The study was carried out as part of the RECAP preterm project, which aims to create a harmonised database of very preterm European birth cohorts to optimise the use of population data for research and innovation.[1]

2 | METHODS

2.1 | Data sources

Data from three European population-based cohorts investigating births below 27 weeks' GA were included. The EXPRESS study comprised births in Sweden between 1 April 2004 and 31 March 2007.[9] Surviving children were followed until 1 year of age and, at 2.5 years corrected age, neurodevelopmental outcomes of 415 out of 481 children known to be alive were assessed by paediatric specialists, ophthalmologists and neuropsychologists; information was available for a further 41 following medical chart review.[10] EPICure-2 studied all births in England between 1 January and 31 December 2006.[11] At 3 years corrected age, of 1029 survivors, 576 children were evaluated by trained paediatricians, data were available from attending paediatrician reports for a further 191, and questionnaire responses were obtained from 523 parents.[12] The EPIPAGE-2 study included births at 22 to 26 weeks' GA in France between 28 March and 31 December 2011.[13] At 2 years corrected age, among the 544 survivors, attending physician reports were available for clinical assessment of 450 children with case review by an independent committee, and parent report data were available for 313 infants.[14]

2.2 | Populations included

We included foetuses alive at maternal admission to hospital, which were subsequently born between 22 and 26 completed weeks' GA

from the three cohorts (i.e., up to 26 weeks and 6 days). Foetuses delivered following termination of pregnancy performed in accordance with national regulatory guidance were excluded (647 in EPICure-2[15] and 188 in EPIPAGE-2[13]; terminations of pregnancy were not permitted beyond 22 weeks' GA in Sweden); we did not exclude babies with antenatally diagnosed congenital malformations.

2.3 | Data harmonisation

Variable definitions from data dictionaries of each cohort were examined in detail to ensure data compatibility: Only variables harmonised across all three cohorts were included (Supplementary Appendix S1, Table S1). We included maternal age (years), presence of diabetes or hypertension before pregnancy, parity (nulliparous or not), pre-eclampsia, any antenatal steroid administration, placental abruption, type of labour onset (spontaneous, induced or none), level of neonatal care provided at the delivery hospital, mode of delivery (vaginal or Caesarean), infant sex, GA at delivery (in completed weeks), birth weight (grams) and the presence of congenital abnormalities (categorised in accordance with cohort guidelines). It was not possible to harmonise all variables across the cohorts due to discrepancies in variable definitions (maternal smoking, other pre-existing maternal illnesses, preterm prolonged rupture of membranes, presence of chorioamnionitis, use of tocolysis and maternal receipt of antibiotics antenatally) or because data were not collected in at least one of the cohorts (socioeconomic classification, maternal ethnicity, and Apgar scores). In addition to age at death for babies that did not survive, we harmonised information on neonatal morbidities: highest grade of intraventricular haemorrhage (using the classification of Papile et al.), cystic periventricular leucomalacia (de Vries et al.), surgical treatment for patent ductus arteriosus or necrotising enterocolitis, bronchopulmonary dysplasia (classified as none or mild; moderate; and severe) and both stage and treatment of retinopathy of prematurity (using the international classification).

As developmental follow-up occurred at different ages using two different developmental tests (the Bayley Scales of Infant and Toddler Development Third Edition, and Ages and Stages Questionnaire Third Edition), we could not directly harmonise data from neurocognitive assessments. However, we report blindness and deafness as binary variables and functional motor level based broadly on the Gross Motor Functional Classification System as no disability or, for those with cerebral palsy: mild disability (GMFCS level 1); moderate disability (GMFCS level 2); and severe disability (GMFCS levels 3 to 5).

2.4 | Outcomes

The primary outcome was survival to 112 days (16 weeks) of postnatal age. Survival to this age was chosen as it is unlikely to be misclassified and to ensure the majority of postnatal deaths were

captured while allowing early differences to be clearly visualised. We also report neonatal morbidity levels among survivors to hospital discharge, post-discharge mortality and neurosensory impairment identified at follow-up at 2 to 3 years corrected age. We assumed that differences in the rates of impairment between follow-up at 2, 2.5 and 3 years of age were negligible as moderate-severe impairments like those examined here have previously been shown to be stable at a population level through to middle childhood.[16]

2.5 | Statistical analysis

Following harmonisation, we compared characteristics of mothers and foetuses alive at maternal admission to hospital between the three cohorts. Breakdowns by GA at delivery, sex, birth weight (<500 grams, and 500 grams or greater) and presence of congenital anomalies are presented alongside neonatal morbidity rates for children discharged alive from hospital; we include a count of the total number of severe morbidities (defined as intraventricular haemorrhage ≥grade 3, cystic periventricular leucomalacia, surgically treated necrotising enterocolitis, retinopathy of prematurity ≥stage 3 and severe bronchopulmonary dysplasia) among survivors at discharge. Survival status and sensorimotor disabilities (vision, hearing and functional motor level) are presented for survivors to follow-up. Differences were examined using the chi-squared test. As lower numbers of babies were born at 22 and 23 weeks, and survival in the EPIPAGE-2 cohort is known to be extremely poor at these gestations,[13] we combined data for births below 24 weeks in all analyses.

Survival to 112 days of age was examined according to week of gestation at birth using Kaplan-Meier analysis on an individual foetus/infant basis with baselines of (a) foetuses alive at maternal admission to hospital, (b) live births, (c) babies surviving to 1 hour of age, (d) 24 hours (1 day) of age, (e) 7 days of age and (f) 28 days of age. Differences between the cohorts were examined using the log-rank test. We verified these results using unadjusted Cox proportional hazards regression conducted for each week of gestation. We then performed Cox proportional hazards regression adjusted for baseline maternal and pregnancy factors, multiple birth, infant sex and birth weight. We did not adjust for obstetric interventions, place or mode of delivery as these have been demonstrated[9,17,18] to be related to perinatal decision-making and are, therefore, intermediate variables between our exposure, the country of each cohort, and survival and other outcomes. Furthermore, the organisation of perinatal care and use of obstetric interventions, in particular Caesarean delivery, vary greatly across countries for reasons that are unrelated to care of extremely preterm birth. We included clustering at the level of the mother using the sandwich estimator in all regression models to account for effects from women with multiple births. The full range of data available was used in the Cox models, with survival status right-censored at cohort follow-up (2.5 years for EXPRESS, 3 years for EPICure-2 and 2 years for EPIPAGE-2) for surviving children. As missing data among included covariates were minimal, we only performed complete case analyses. The proportional hazards assumption was assessed by examining chi-squared tests of scaled Schoenfeld residuals.

All analyses were performed in R (version 3.5.2) and reported according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Supplementary Appendix S1, Table S2) using 95% confidence intervals (95% CI).

2.6 | Sensitivity analyses

Because outcomes may differ between singleton and multiple births, we repeated the adjusted Cox proportional hazards models using births from singleton pregnancies only.

3 | RESULTS

In EXPRESS, 769 of 1011 (76.1%) foetuses were alive at admission for delivery (687 women), in EPICure-2, 2310 of 3132 (73.8%) foetuses were alive at admission for delivery (1649 women), and in EPIPAGE-2, 1359 of 2205 (61.6%) foetuses were alive at admission for delivery (1135 women).

3.1 | Maternal characteristics

Women were more often younger (under 25 years old) and primiparous in EPICure-2 compared with either of the other two cohorts ($p < 0.001$ for both variables for the differences between the cohorts). Although there were no differences in the prevalence of pre-existing diabetes or hypertension, more women were diagnosed with pre-eclampsia in EXPRESS. Full results are shown in Table 1.

3.2 | Foetal characteristics

Characteristics of the 4438 foetuses alive at maternal admission to hospital are shown in Table 2, with a breakdown by GA group in Supplementary Appendix S1, Tables S4 and S5. The proportion of births from multiple pregnancies varied from 22.0% in EXPRESS to 25.5% in EPICure-2 and 31.2% in EPIPAGE-2, whereas placental abruption was more commonly diagnosed in EXPRESS. Foetuses in EXPRESS and EPICure-2 were more likely to be exposed to antenatal steroids compared with those in EPIPAGE-2 and to be born in a tertiary unit in EXPRESS and EPIPAGE-2, and by Caesarean delivery in EXPRESS. Differences between cohorts were seen in the GA distribution ($p = 0.002$) but not in birth weight distribution or sex ratios; congenital anomalies were

TABLE 1 Baseline data for 3876 mothers with a live foetus at admission to hospital in the EXPRESS (Sweden, 2004–06), EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts

Variable Levels	EXPRESS		EPICure-2		EPIPAGE-2		p-value
	n	%	n	%	n	%	
Maternal age (years)							
<25	108	15.8	575	28.3	274	23.8	<0.001
25–34	384	56.3	1028	50.6	668	58.1	
≥35	190	27.9	429	21.1	208	18.1	
Missing	5	–	4	–	3	–	
Parity							
Nullipara	270	39.3	979	48.6	481	42.1	<0.001
Para 1+	417	60.7	1034	51.4	661	57.9	
Missing	0	–	23	–	11	–	
Pre-existing diabetes							
No	644	98.8	2010	98.8	1118	99.1	0.709
Yes	8	1.2	24	1.2	10	0.9	
Missing	35	–	2	–	25	–	
Pre-existing hypertension							
No	662	96.4	1978	97.2	1117	96.9	0.579
Yes	25	3.6	58	2.8	36	3.1	
PIH/PE							
No	613	89.2	1906	93.6	1071	92.9	<0.001
Yes	74	10.8	130	6.4	82	7.1	
Onset of labour							
Spontaneous	518	76.5	1709	84.4	872	77.4	<0.001
Induced	12	1.8	83	4.1	43	3.8	
None	147	21.7	234	11.5	211	18.7	
Missing	10	–	10	–	27	–	

Note: Percentages may not equal 100 due to rounding.

Abbreviations: PE: pre-eclampsia; PIH: pregnancy-induced hypertension.

more frequently reported in EXPRESS compared with EPICure-2 or EPIPAGE-2.

3.3 | Kaplan-Meier analysis

Kaplan-Meier survival curves for babies born at 22–23 weeks (Figure 1) highlight that survival was substantially higher in EXPRESS than either EPICure-2 or EPIPAGE-2; only two of 366 babies born in EPIPAGE-2 below 24 weeks gestation survived to 112 days, and one of these subsequently dying before hospital discharge. Differences in outcome between EXPRESS and EPICure-2 are also apparent using each of the baseline populations; for example, of babies surviving to 28 days who were born at 22–23 weeks, only 78% (73 of 93 babies) survived in EPICure-2 compared to 97% (59 of 61) babies in EXPRESS. At 24 weeks (Figure 2), survival varied between the three cohorts based on the populations of foetuses alive at the maternal delivery admission, live births and of the babies who survived to 1 and 24 hours of age, being highest in EXPRESS and lowest

in EPIPAGE-2. From 24 hours, survival in EPICure-2 and EPIPAGE-2 converged but remained lower than in EXPRESS. Survival was higher in all three countries at 25 weeks of gestation (Figure 3): with differences between cohorts less marked and no differences among babies who survived to 28 days postnatal age. At 26 weeks (figure 4), there were small but consistent early differences between cohorts up to 24 h of age, but no important differences thereafter.

3.4 | Cox regression

Hazard ratios (HRs) were consistent with results from Kaplan-Meier analyses (Table 3). Following adjustment for baseline maternal and offspring characteristics, differences between the cohorts became even more pronounced at 22–23 weeks of gestation, but at 24, 25 and 26 weeks, there were few differences between adjusted and unadjusted results. The assessment of proportionality (Supplementary Appendix S1, Table S3) demonstrated that some variations in HRs existed across the time points used for the

TABLE 2 Baseline data for 4438 foetuses alive at maternal admission to hospital from the EXPRESS (Sweden, 2004–06), EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts

	EXPRESS		EPICure-2		EPIPAGE-2		
Variable Levels	n	%	n	%	n	%	p-value
Level of neonatal care at delivery hospital							
1	20	2.6	217	9.5	87	6.4	<0.001
2	152	19.9	757	33.2	290	21.3	
3	590	77.4	1304	57.2	982	72.3	
Missing	7	–	32	–	0	–	
Exposure to antenatal steroids							
No	125	17.0	649	28.3	610	46.7	<0.001
Yes	612	83.0	1641	71.7	695	53.3	
Missing	32	–	20	–	54	–	
Placental abruption							
No	641	88.8	2137	93.0	1278	96.1	<0.001
Yes	81	11.2	161	7.0	52	3.9	
Missing	47	–	12	–	29	–	
Multiple birth							
No	600	78.0	1721	74.5	935	68.8	<0.001
Yes	169	22.0	589	25.5	424	31.2	
Delivery type							
Vaginal	413	53.7	1800	78.1	933	70.4	<0.001
Caesarean	356	46.3	505	21.9	392	29.6	
Missing	0	–	5	–	34	–	
Gestational age at delivery (weeks)							
22	89	11.6	262	11.3	171	12.6	0.002
23	120	15.6	413	17.9	195	14.3	
24	146	19	493	21.3	246	18.1	
25	205	26.7	548	23.7	325	23.9	
26	209	27.2	594	25.7	422	31.1	
Missing	0	–	0	–	0	–	
Sex							
Male	420	54.7	1218	52.8	732	54.0	0.609
Female	348	45.3	1088	47.2	624	46.0	
Missing	1	–	4	–	3	–	
Birth weight (g)							
<500	91	12	260	11.3	142	10.7	0.678
≥500	668	88	2031	88.7	1180	89.3	
Missing	10	–	19	–	37	–	
Congenital anomalies							
No	690	89.7	2190	97.8	1335	98.4	<0.001
Yes	79	10.3	50	2.2	22	1.6	
Missing	0	–	70	–	2	–	

Note: Percentages may not equal 100 due to rounding.

Abbreviation: g, grams.

baseline populations. At 22–23 weeks, these were most apparent in HRs for EPICure-2 up to 1 hour of age, and at 24 weeks in EPICure-2 up to 1 day of age and across the whole time span for EPIPAGE-2. There were few apparent differences between the three cohorts at 25 or 26 weeks.

3.5 | Sensitivity analyses

Among singleton pregnancies, results were generally consistent with the main analyses with similar effect sizes albeit wider confidence intervals. Compared with EXPRESS, there were no differences at

22–23 weeks of gestation

FIGURE 1 Survival curves for the EXPRESS (Sweden, 2004–07), EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts for foetuses born at 22–23 completed weeks of gestational age

24 weeks of gestation

FIGURE 2 Survival curves for the EXPRESS (Sweden, 2004–07), EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts for foetuses born at 24 completed weeks of gestational age

FIGURE 3 Survival curves for the EXPRESS (Sweden, 2004–07), EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts for foetuses born at 25 completed weeks of gestational age

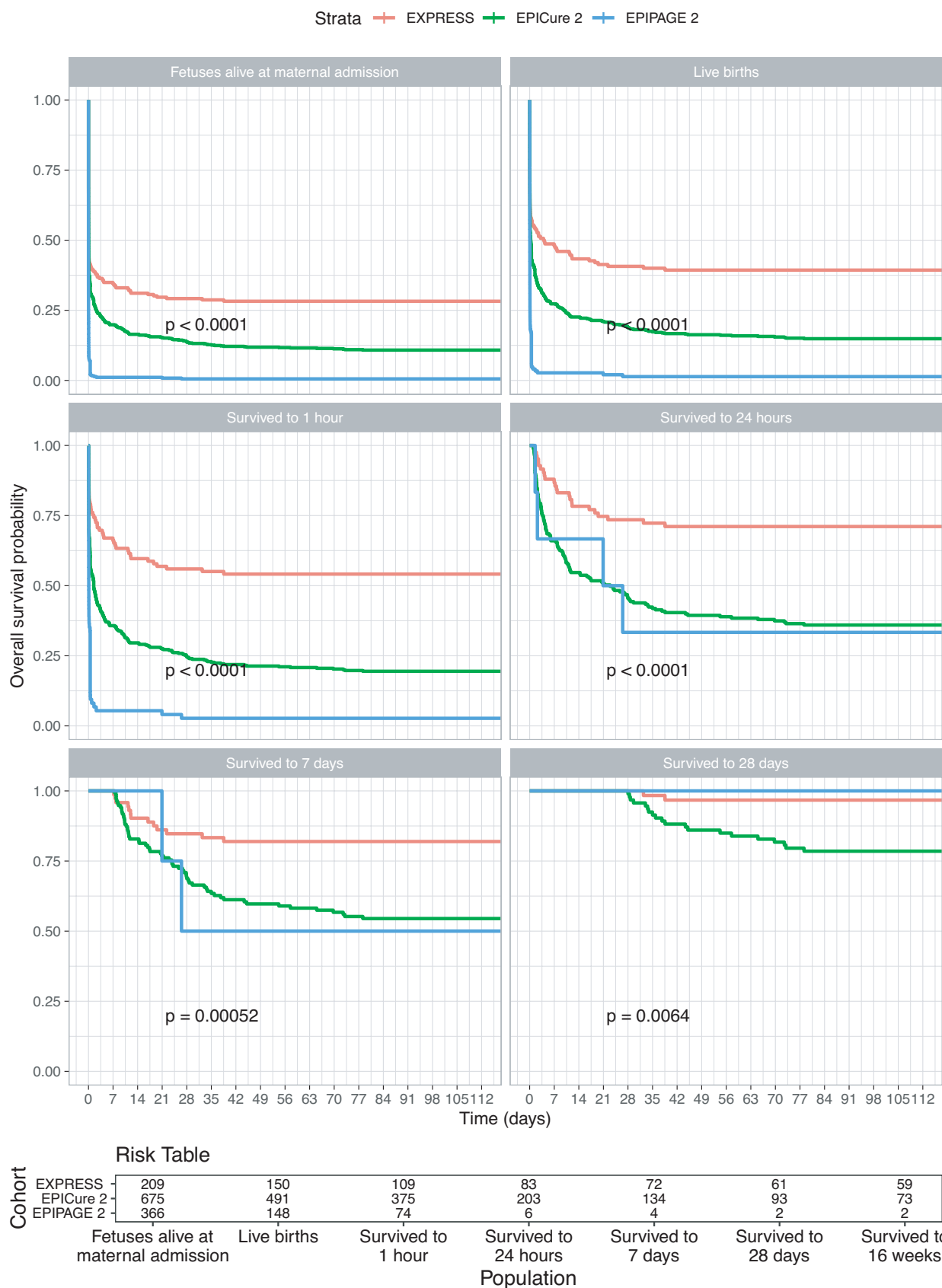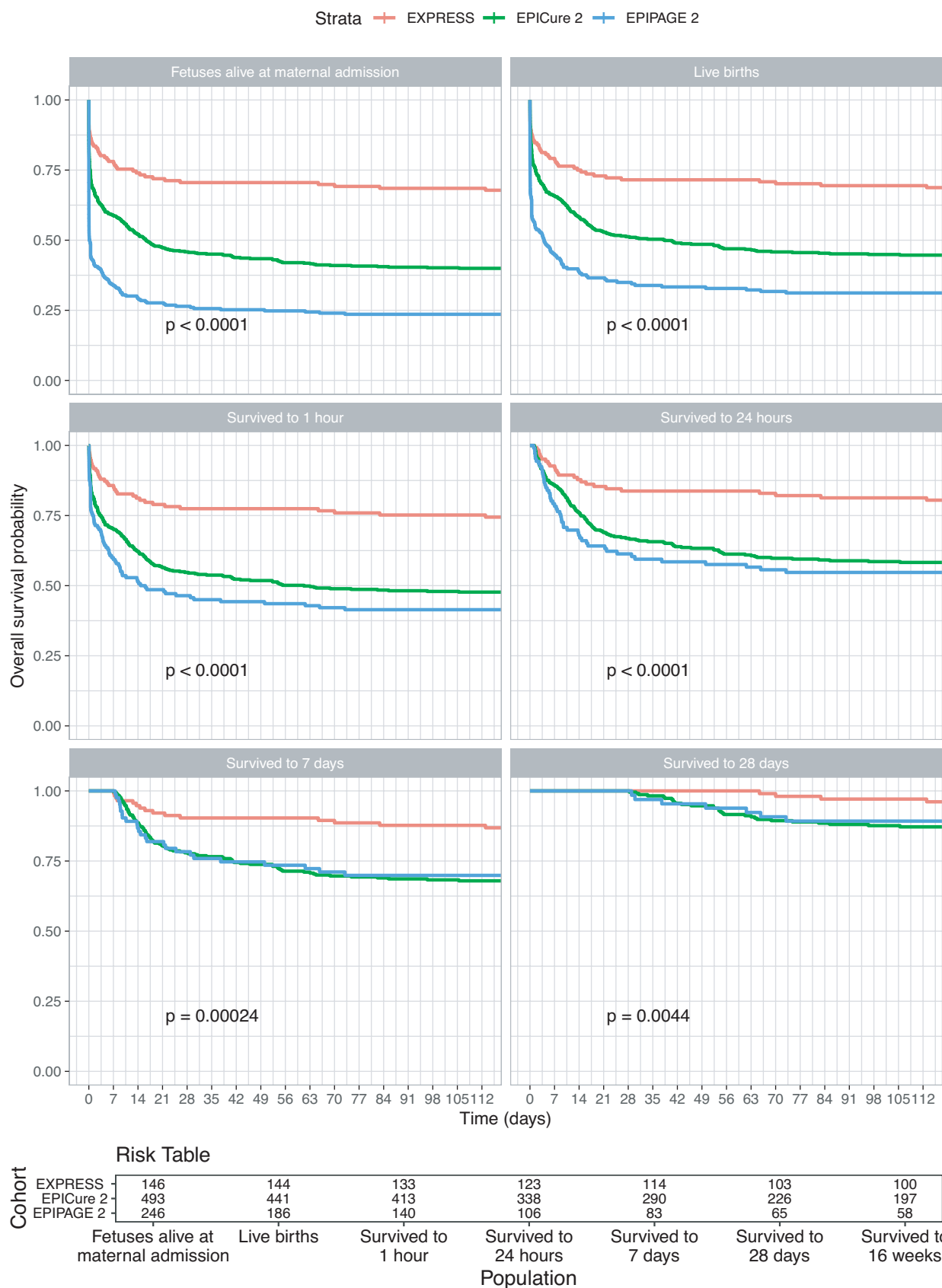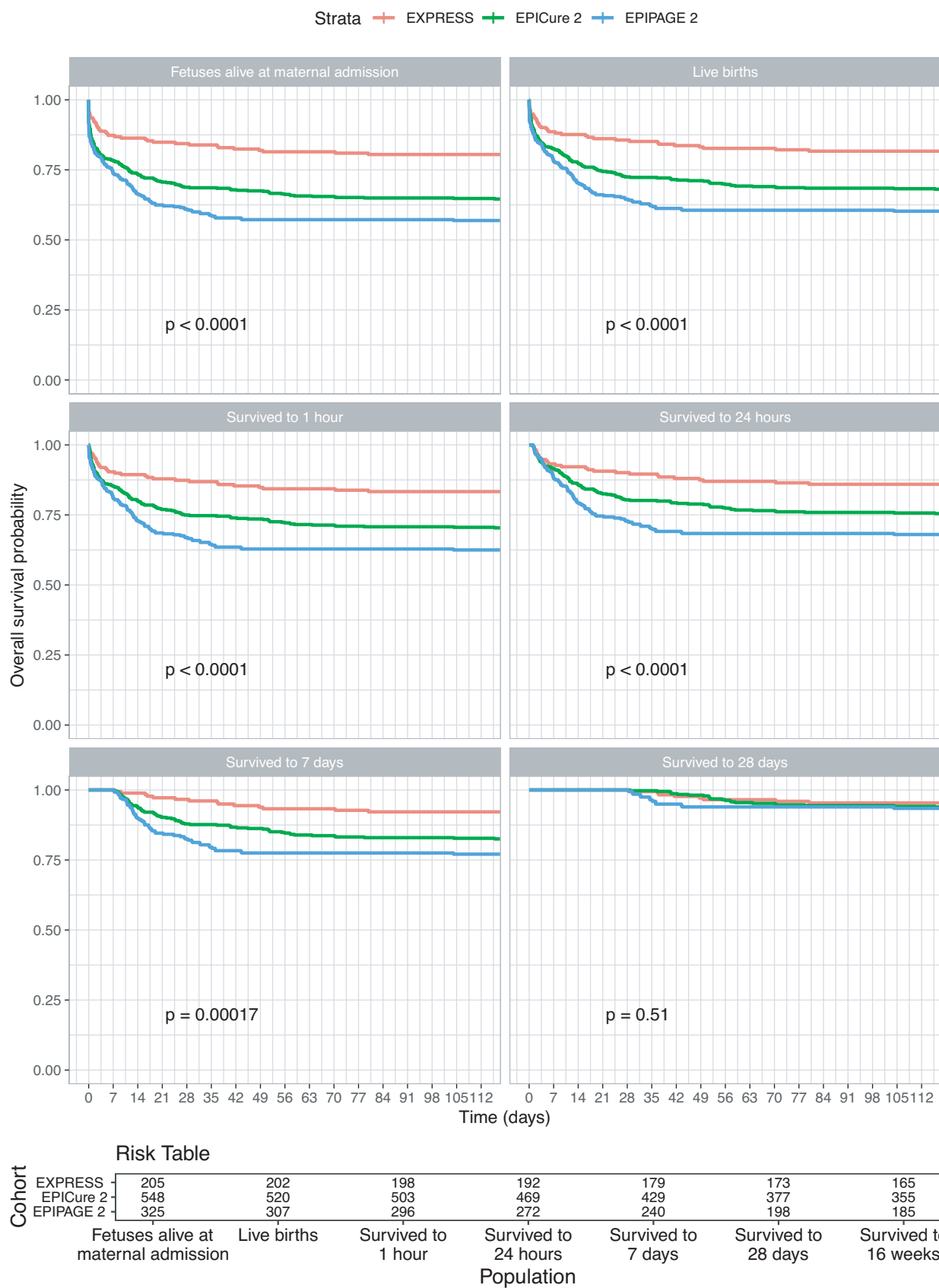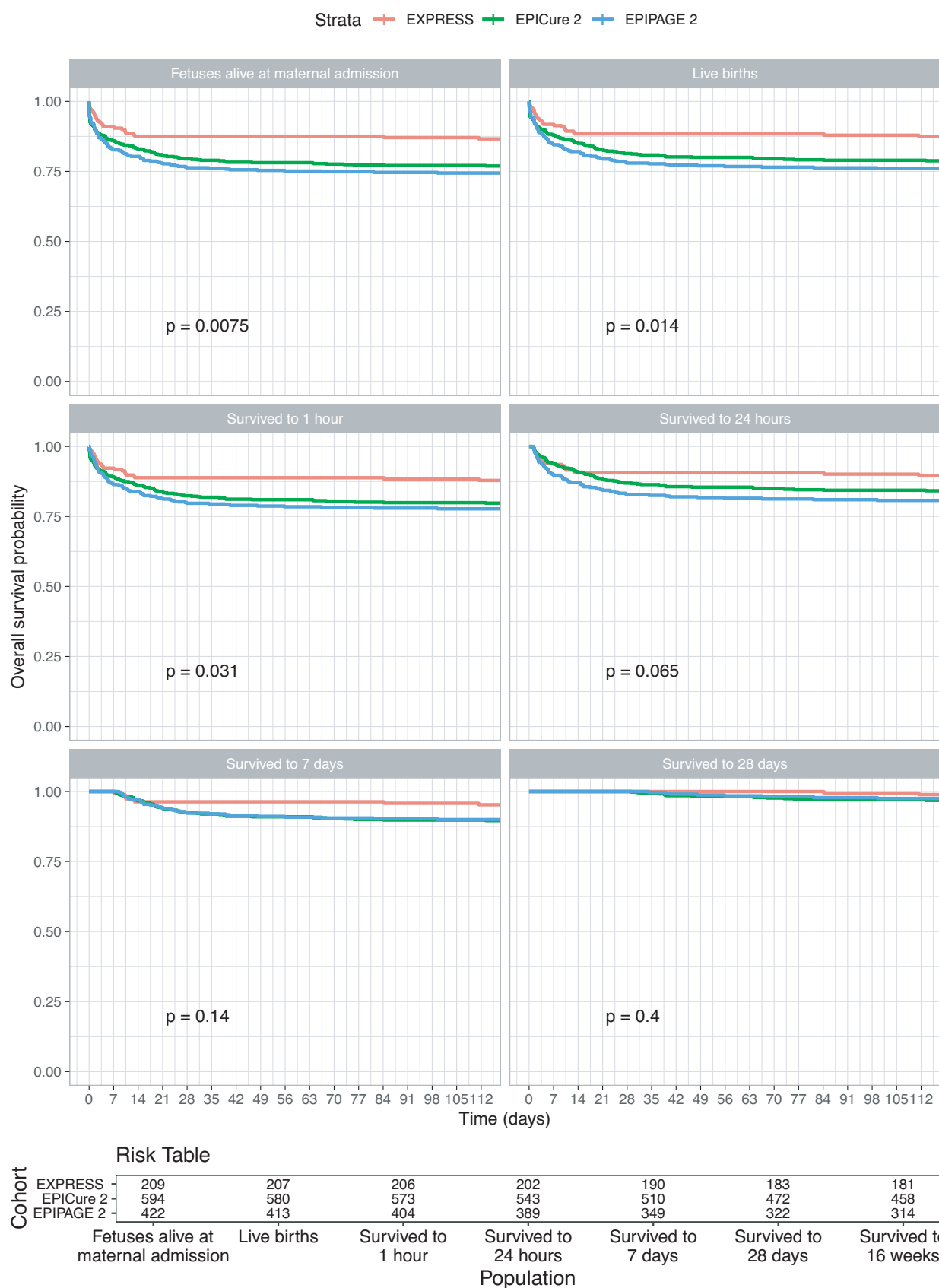**FIGURE 4** Survival curves for the EXPRESS (Sweden, 2004–07), EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts for foetuses born at 26 completed weeks of gestational age

TABLE 3 Hazard ratios for mortality of babies born extremely preterm in the EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts in comparison with EXPRESS (Sweden, 2004–07) according to different baseline populations; unadjusted results and results adjusted for maternal age, parity, pre-existing diabetes and hypertension, pre-eclampsia, placental abruption, spontaneous labour, multiple pregnancy, sex and birth weight

| | | Unadjusted HRs | | | | | Adjusted HRs | | | | |
| | | EPICure-2 | | | EPIPAGE-2 | | EPICure-2 | | | EPIPAGE-2 | |
GA	Population	n	HR	(95% CI)	HR	(95% CI)	n	HR	(95% CI)	HR	(95% CI)
22–23	Foetuses alive at maternal admission	1250	1.42	(1.15–1.75)	3.76	(2.99–4.71)	1141	1.44	(1.15–1.80)	3.91	(3.04–5.02)
	Live births	789	1.73	(1.33–2.24)	4.62	(3.39–6.29)	751	1.75	(1.31–2.34)	5.07	(3.57–7.19)
	Survived to 1 hour	558	2.48	(1.81–3.41)	7.20	(4.80–10.80)	537	2.45	(1.75–3.44)	7.65	(4.82–12.13)
	Survived to 1 day	292	2.84	(1.80–4.48)	3.71	(1.61–8.60)	287	2.79	(1.74–4.45)	4.66	(1.74–12.47)
	Survived to 7 days	210	2.76	(1.48–5.16)	4.41	(1.60–12.17)	208	2.87	(1.47–5.62)	4.66	(1.79–12.13)
	Survived to 28 days	156	4.46	(1.56–12.74)	8.42	(1.34–52.79)	155	5.93	(1.65–21.30)	14.55	(2.70–78.25)
24	Foetuses alive at maternal admission	885	2.29	(1.69–3.08)	3.97	(2.85–5.51)	840	2.10	(1.53–2.88)	3.59	(2.52–5.10)
	Live births	771	2.06	(1.50–2.82)	3.16	(2.21–4.52)	739	1.94	(1.39–2.69)	2.94	(2.01–4.30)
	Survived to 1 hour	686	2.46	(1.76–3.43)	2.83	(1.91–4.18)	661	2.29	(1.61–3.24)	2.51	(1.65–3.81)
	Survived to 1 day	567	2.43	(1.63–3.62)	2.48	(1.54–4.01)	548	2.21	(1.47–3.33)	2.09	(1.26–3.46)
	Survived to 7 days	487	2.64	(1.63–4.27)	2.06	(1.12–3.76)	470	2.58	(1.57–4.25)	1.83	(0.96–3.49)
	Survived to 28 days	394	2.97	(1.41–6.22)	1.46	(0.53–4.07)	381	2.92	(1.36–6.25)	1.46	(0.51–4.19)
25	Foetuses alive at maternal admission	1078	2.02	(1.44–2.84)	2.56	(1.79–3.64)	1040	1.96	(1.36–2.81)	2.45	(1.68–3.57)
	Live births	1029	1.90	(1.33–2.72)	2.46	(1.69–3.57)	994	1.86	(1.27–2.73)	2.31	(1.55–3.44)
	Survived to 1 hour	997	1.93	(1.32–2.82)	2.54	(1.71–3.77)	964	1.88	(1.24–2.83)	2.39	(1.56–3.66)
	Survived to 1 day	933	1.86	(1.23–2.81)	2.49	(1.62–3.84)	902	1.89	(1.22–2.94)	2.42	(1.53–3.83)
	Survived to 7 days	848	2.34	(1.39–3.96)	3.10	(1.78–5.39)	821	2.19	(1.25–3.87)	2.93	(1.63–5.28)
	Survived to 28 days	748	1.48	(0.73–3.00)	1.52	(0.68–3.38)	725	1.60	(0.70–3.66)	1.85	(0.73–4.64)
26	Foetuses alive at maternal admission	1225	1.70	(1.15–2.51)	1.85	(1.24–2.76)	1172	1.76	(1.16–2.66)	1.92	(1.26–2.93)
	Live births	1200	1.64	(1.10–2.47)	1.82	(1.20–2.76)	1147	1.74	(1.13–2.66)	1.88	(1.22–2.90)
	Survived to 1 hour	1183	1.62	(1.07–2.45)	1.72	(1.12–2.65)	1131	1.73	(1.12–2.69)	1.78	(1.13–2.78)
	Survived to 1 day	1134	1.43	(0.90–2.27)	1.70	(1.06–2.72)	1085	1.53	(0.94–2.50)	1.76	(1.07–2.88)
	Survived to 7 days	1049	1.82	(1.01–3.30)	1.63	(0.87–3.06)	1003	1.68	(0.88–3.19)	1.43	(0.74–2.77)
	Survived to 28 days	977	1.58	(0.65–3.82)	1.05	(0.39–2.83)	932	1.48	(0.53–4.16)	0.81	(0.28–2.37)

Abbreviations: CI: confidence interval; GA, gestational age (weeks) at delivery; HR, hazard ratio.

25 weeks after 7 days of age for EPICure-2 or EPIPAGE-2, and at 26 weeks after 1 hour for EPICure-2 and 1 day for EPIPAGE-2. Full results are shown in Supplementary Appendix S1, Tables S10 and S11.

3.6 | Neonatal outcomes at discharge

Overall, 2088 children were discharged alive from hospital: among live births, 497 of 702 (70.8%) in the EXPRESS cohort, 1040 of 2017 (51.6%) in EPICure-2 and 551 of 1046 (52.7%) in EPIPAGE-2. The prevalence of neonatal morbidities varied between the three cohorts, as shown in Table 4. For example, the highest grades of intraventricular haemorrhage and surgically treated necrotising enterocolitis were reported in EPICure-2, whereas the highest rates of surgically treated patent ductus arteriousus were reported by EXPRESS. EPIPAGE-2 had the lowest rates of stage 3 or higher retinopathy, cystic periventricular leukomalacia and moderate or severe bronchopulmonary dysplasia. Few children who survived to discharge had more than one severe neonatal morbidity, although this figure was notably higher in EPICure-2. Severity of both bronchopulmonary dysplasia and retinopathy of prematurity increased with decreasing GA (Supplementary Appendix S1, Tables S6 and S7) but, in general, neonatal outcomes were consistent across GA groups.

3.7 | Post-discharge outcomes

Death between discharge and initial follow-up was similar across the three cohorts: 2.2% in EXPRESS (five children had no data available due to emigration or having a protected identity), 1.1% in EPICure-2 and 1.3% in EPIPAGE-2 ($p = 0.178$). At 2 to 3 years of age, among children with available data, there were similar proportions with blindness or deafness in the three cohorts. The proportions of children categorised with severe motor impairment (GMFCS levels 3 to 5) were similar in EXPRESS and EPIPAGE-2 but markedly higher in EPICure-2, and there was also an excess of children diagnosed with mild cerebral palsy (GMFCS level 1) in EPICure-2 compared with EXPRESS and EPIPAGE-2; full details are in Table 5. Results were again broadly similar across the gestational age range (Supplementary Appendix S1, Tables S8 and S9).

4 | DISCUSSION

This comparative analysis of three population-based extremely preterm birth cohorts found important differences in survival using different baseline populations up to and including that of babies who survived to 28 days of age. At 22–23 and 24 weeks of gestation, differences were evident even when comparing survival among the populations of babies surviving to 28 days of age, at 25 weeks, differences existed to 7 days of age and, at 26 weeks, they were evident up to 24 hours of age. EXPRESS had the highest survival and the best motor outcomes at follow-up; survival was generally better in EPICure-2 than EPIPAGE-2, but the proportion with neonatal morbidities and children categorised with cerebral palsy was more frequent.

4.1 | Strengths and limitations

International comparisons of outcomes for extremely preterm births are difficult. This study's strengths are that we compared three large national prospective population-based cohorts using individual patient-level data with harmonisation of both inclusion criteria and individual variables, thus enabling us to overcome pitfalls such as discrepancies in population baseline or variable definitions[19] that may have affected other comparisons.[20] Minimal missing data for the included variables (including none for survival) and effective statistical methods provide confidence that remaining differences are not explained by included characteristics. We were, however, limited in the variables we could harmonise. There was no common socioeconomic measure - although previously deprivation has only been related to rates of preterm birth and not to perinatal survival[21] - nor was there common information about maternal ethnicity or country of birth. We lacked indicators relating to condition at birth such as the CRIB, CRIB-II or Apgar scores, nor did we have information about delivery room or neonatal practices, and we could not compare cognitive outcomes at follow-up.

Despite careful harmonisation, some potential differences remained among included variables. For example, we did not have detailed information relating to how gestational age was determined, and we know that there are differences between countries. In England and France, determination is usually with first-trimester ultrasound, although it also occurs using time since last menstrual period, whereas in Sweden, at the time of the EXPRESS study, dating was performed around 18 weeks. This could be less accurate, leading to increased variance around the estimated gestation but would be unlikely to alter the mean. When we compared relationships between GA and birth weight, we found no differences between cohorts (data not shown). Another difference related to congenital anomalies, which were higher in EXPRESS. National policies on termination of pregnancy varied between the countries. In both EPICure-2 and EPIPAGE-2, a majority of terminations are performed for foetal anomalies[15,22]; this might imply higher survival rates than EXPRESS, but we found the inverse. We believe the different rates seen for congenital anomalies are most likely due to residual differences in harmonisation, as shown in Supplementary Appendix S1, Table S1, hence why they are not related to survival.

4.2 | Interpretation

We provide strong evidence of survival differences between the three cohorts. Furthermore, testing of the proportional hazards assumption demonstrated variation in HRs over time. Such variation can be assessed using an interaction for time in the models or, as we

TABLE 4 Data from the EXPRESS (Sweden, 2004–06), EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts for babies who were discharged alive from hospital

	EXPRESS		EPICure-2		EPIPAGE-2		
Variable Levels	n	%	n	%	n	%	p-value
Gestational age at delivery (weeks)							
23	58	11.7	69	6.6	1	0.2	<0.001
24	95	19.1	178	17.1	58	10.5	
25	164	33	345	33.2	181	32.8	
26	180	36.2	448	43.1	311	56.4	
Sex							
Male	270	54.3	505	48.6	280	50.8	0.105
Female	227	45.7	535	51.4	271	49.2	
Birth weight (g)							
<500 g	18	3.6	12	1.2	4	0.7	<0.001
≥500 g	479	96.4	1028	98.8	547	99.3	
Congenital anomalies							
No	442	88.9	1004	98.9	545	98.9	<0.001
Yes	55	11.1	11	1.1	6	1.1	
Missing	0	–	25	–	0	–	
Highest grade of IVH							
0	310	62.9	490	47.3	286	51.9	<0.001
1	89	18.1	170	16.4	93	16.9	
2	45	9.1	188	18.2	126	22.9	
3	26	5.3	54	5.2	29	5.3	
4	23	4.7	133	12.9	17	3.1	
Missing	4	–	5	–	0	–	
Cystic PVL							
No	469	94.4	976	94.3	538	97.6	0.008
Yes	28	5.6	59	5.7	13	2.4	
Missing	0	–	5	–	0	–	
PDA treated surgically							
No	362	72.8	867	83.9	406	76.0	<0.001
Yes	135	27.2	166	16.1	128	24.0	
Missing	0	–	7	–	17	–	
NEC treated surgically							
No	476	96.9	961	92.4	526	95.5	<0.001
Yes	15	3.1	79	7.6	25	4.5	
Missing	6	–	0	–	0	–	
Bronchopulmonary dysplasia							
None/mild	142	31.3	323	31.1	304	60.8	<0.001
Moderate	199	43.9	291	28.0	64	12.8	
Severe	112	24.7	425	40.9	132	26.4	
Missing	44	–	1	–	51	–	
Treated ROP							
No	124	52.5	474	74.1	330	94.0	<0.001
Yes	112	47.5	166	25.9	21	6.0	
Missing	261	–	400	–	200	–	
ROP stage							
0	137	27.8	393	38.0	186	52.2	<0.001

(Continues)

TABLE 4 (Continued)

Variable Levels	EXPRESS n	%	EPICure-2 n	%	EPIPAGE-2 n	%	p-value
1	75	15.2	198	19.2	77	21.6	
2	112	22.8	229	22.2	65	18.3	
3	162	32.9	209	20.2	27	7.6	
4	3	0.6	3	0.3	1	0.3	
5	3	0.6	1	0.1	0	0.0	
Missing	5	–	7	–	195	–	
Total number of neonatal morbidities							
0	231	46.5	410	39.4	348	63.2	<0.001
1	180	36.2	373	35.9	165	29.9	
2	68	13.7	188	18.1	35	6.4	
3	16	3.2	62	6.0	3	0.5	
4	2	0.4	7	0.7	0	0.0	
Missing	0	–	0	–	0	–	

Note: Total neonatal morbidities: IVH ≥ grade III, PVL, surgically treated NEC, ROP ≥ stage 3, severe bronchopulmonary dysplasia.

Abbreviations: IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

TABLE 5 Data for babies from the EXPRESS (Sweden, 2004–06), EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts who were discharged alive from hospital and survived to follow-up

Variable Levels	EXPRESS n	%	EPICure-2 n	%	EPIPAGE-2 n	%	p-value
Survived to follow-up*							
Yes	481	97.8	1029	98.9	544	98.7	0.178
No	11	2.2	11	1.1	7	1.3	
Blind							
No	451	99.1	569	99	418	99.5	0.615
Yes	4	0.9	6	1.0	2	0.5	
Missing	26	–	454	–	124	–	
Deaf							
No	442	99.8	574	99.8	441	100	0.632
Yes	1	0.2	1	0.2	0	0.0	
Missing	38	–	454	–	103	–	
Functional motor impairment level (GMFCS)							
None	423	93.0	591	78.7	418	93.1	<0.001
Mild (GMFCS 1)	13	2.9	90	12.0	11	2.4	
Moderate (GMFCS 2)	13	2.9	27	3.6	12	2.7	
Severe (GMFCS 3–5)	6	1.3	43	5.7	8	1.8	
Missing	26	–	278	–	95	–	

Abbreviations: GMFCS, Gross Motor Functional Classification System.

*Five children from EXPRESS had emigrated or had a protected identity at 2.5 years of age, hence survival information was not available; they have been excluded from this table.

did, by varying the baseline population. HRs decreased for all GA groups as the starting point became later, indicating that the most important differences occur early on. We investigated model differences by examining p-values for individual HRs and the overall model. Compared with EXPRESS, variation was related more to differences with EPIPAGE-2 than EPICure-2. Importantly, differences persisted beyond just the antenatal or delivery-room periods and into the first days and weeks after birth. This supports the hypothesis

that variations in survival are not only due to decisions occurring antenatally and around the time of birth, but that they might evolve over time and relate to adverse events occurring at later time points in the neonatal period and infancy.

Neonatal morbidity patterns are more difficult to explain. Some might be expected: the higher proportions of survivors at 22 to 24 weeks in EXPRESS and EPICure-2 could be linked to increased need for more aggressive ventilatory management, thus explaining the higher proportion of moderate-severe bronchopulmonary dysplasia, periventricular leukomalacia and retinopathy stages 3–5 seen in these cohorts. The pattern of rising retinopathy of prematurity and falling mortality is similar to that seen in the recent oxygen saturation targeting trials,[23] but the close relationship between the prevalence of retinopathy and gestational age means that retinopathy becomes more frequent as survival increases. However, increased survival of less mature babies also leads to more retinopathy independently of oxygen targets. Lower levels of surgically treated necrotising enterocolitis in EXPRESS and EPIPAGE-2 might be associated with increased use of individual rooms in Sweden and France, perhaps mediated by the availability of maternal breast milk.[24] A more recent cohort - the EXPRESS 2 - study found neonatal morbidities in 22–24 week infants were reduced by half, underlining the potential role of neonatal management.[25] However, we did not have data available to investigate these hypotheses.

Following discharge from hospital, survival did not differ between the cohorts, but numbers are low and consequently the power to examine this is lacking: the higher post-discharge mortality seen in EXPRESS thus may be either due to chance or related to Swedish policy. Morbidity status at 2–3 years of age is also difficult to interpret as there were no clear relationships between survival and levels of morbidity. Few children suffer from blindness or deafness hence again, no statistical differences were seen. Knowledge about functional motor status was most complete in EXPRESS, with impairment rates lower than the other cohorts; however, substantial data were missing in both EPICure-2 and EPIPAGE-2. The excess numbers of children diagnosed with cerebral palsy in EPICure-2 compared to the other two cohorts is noteworthy. This might be related to missing data or to differences between countries in end-of-life decision-making. It could also reflect different approaches to diagnosis: In EPICure-2, categorisations were made by the research team based on recorded neurological assessments by trained assessors[12]; for EXPRESS and EPIPAGE-2, diagnoses were provided by paediatricians or paediatric neurologists.[10,14] Differences in follow-up age may also have had an impact.

4.3 | Generalisability

Using harmonised inclusion criteria and definitions, this study confirms previous research documenting wide variation in survival for extremely preterm births. It extends our knowledge by showing that these survival differences, while most marked perinatally, persist over time during the first hours, days and weeks after birth,

particularly for the most preterm babies, and that population characteristics or methodological differences do not contribute to explaining them. The results also demonstrate that the relationships between 'early selection' and later outcomes are complex - even in terms of survival, higher mortality around birth does not appear to identify a subset of babies who are subsequently more likely to live; the relationships with neonatal morbidity and longer term neurosensory outcomes are likewise complex.

We attribute these findings to variations in decision-making attitude and believe that such variation between countries is likely to have remained similar over time. At a societal level, different decisions are reached regarding factors such as the centralisation of care, provision of parental support, and availability and type of follow-up programs. For example, the lower rate of delivery in level 3 units in the EPICure-2 cohort may have contributed to higher rates of cerebral palsy than in the EXPRESS and EPIPAGE-2 cohorts. The risk of intraventricular haemorrhage, the single most important cause of cerebral palsy in extremely preterm infants, has been reported to increase if infants below 28 weeks were born outside a tertiary hospital in England.[26] However, this relationship is complex as seen by highly contrasting survival in the EXPRESS and EPIPAGE-2 cohorts where there were similar proportions of births in hospitals with a level 3 neonatal unit (77.4% and 72.3%, respectively). In Sweden, England and France, management practices since the inception of these cohorts have evolved towards less aggressive handling at birth, avoidance of mechanical ventilation where possible, more effective ventilation and better parent engagement, including skin-to-skin care and family rooms in the intensive care unit. Combinations of subtle improvements may lead to improvements in survival: EXPRESS 2 recently reported improved survival compared with the first EXPRESS study,[25] optimum antenatal care combined with active postnatal management has been associated with improved survival,[27] and previous studies (including based on data from EXPRESS and EPIPAGE-2) demonstrate that more active treatment is associated with higher survival.[2–4] The impact of these practices on long-term morbidity outcomes is less clear, however. This is reflected in differences between guidelines for perinatal management of extremely preterm birth recently published in Sweden,[28] England[29] and France.[30] Further investigation, including cognitive and quality of life outcomes also, is warranted and should take into consideration practices which may explain variation such as that we identified.

5 | CONCLUSION

Differences between the EXPRESS, EPICure-2 and EPIPAGE-2 cohorts in the survival of extremely preterm births to 112 days chronological age are evident despite the use of different baseline populations and adjustment for maternal and foetal characteristics. Neonatal morbidities and neurological outcomes at 2 to 3 years of age also varied between the three cohorts. While it is possible these findings could be explained by socioeconomic or ethnic

discrepancies, this explanation is unlikely to account for all the variation seen. One of the major remaining explanations for these differences is the variation in societal choices between the three countries.

CONFLICT OF INTERESTS

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Morgan AS, Zeitlin J, Källén K, et al. Birth outcomes between 22 and 26 weeks' gestation in national population-based cohorts from Sweden, England and France. Acta Paediatr. 2022;111:59–75. https://doi.org/10.1111/apa.16084