Birth outcomes between 22 to 26 weeks' gestation in national population-based cohorts from Sweden, England and France – supplementary appendix S1

Andrei S. Morgan PhD[a,b,c,*], Jennifer Zeitlin PhD[a], Karin Källén PhD[d], Elizabeth S. Draper PhD[e], Karel Maršál PhD[f], Mikael Norman PhD[g,h], Fredrik Serenius PhD[i], Stef van Buuren PhD[j,k], Samantha Johnson PhD[e], Valérie Benhammou PhD[a], Véronique Pierrat PhD[a], Monique Kaminski MSc[a], Laurence Foix L'Helias PhD[a,l,m], Pierre-Yves Ancel PhD[a,n], Neil Marlow FMedSci[b]

[a] *Université de Paris, CRESS, Obstetrical Perinatal and Pediatric Epidemiology Research Team, EPOPé, INSERM, INRAE, F-75004, Paris, France*
[b] *UCL Elizabeth Garrett Anderson Institute for Women's Health London, University College London, London, UK*
[c] *Department of Neonatology, Maternity Port Royal, Assistance Publique – Hôpitaux de Paris, Paris, France.*
[d] *Centre of Reproductive Epidemiology, Lund University, Lund, Sweden*
[e] *Department of Health Sciences, University of Leicester, Leicester, UK*
[f] *Department of Obstetrics and Gynecology, Lund University, Skåne University Hospital, Lund, Sweden*
[g] *Division of Pediatrics, Department of Clinical Science, Intervention, and Technology, Karolinska Institutet, Stockholm, Sweden*
[h] *Department of Neonatal Medicine, Karolinksa University Hospital, Stockholm, Sweden*
[i] *Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden*
[j] *Netherlands Organisation for Applied Scientific Research TNO, Leiden, Netherlands*
[k] *Methodology & Statistics, Utrecht University, Utrecht, Netherlands*
[l] *Sorbonne University, Paris, France*
[m] *Department of Neonatal Pediatrics, Trousseau Hospital, Assistance Publique – Hôpitaux de Paris, Paris, France.*
[n] *Assistance Publique – Hôpitaux de Paris, Clinical Investigation Center P1419, Assistance Publique-Hôpitaux de Paris, Paris, France*

Abstract

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Contents

1. Contributors

ASM: Design of the study, data preparation, data harmonisation, statistical analysis, interpretation of results, initial draft of the manuscript, critical revision, redrafting and incorporation of comments into revisions, and final approval; ASM is the guarantor, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. **JZ:** Design of the study, interpretation of results, critical revision of the article, and redrafting and final approval of the version to be published. **KK:** Data acquisition, data preparation, data harmonisation, interpretation of results, critical revision of the article and final approval of the version to be published. **ESD:** Data acquisition, data harmonisation, interpretation of results, critical revision of the article and final approval of the version to be published. **KM:** Concept and design of the study, data acquisition, data harmonisation, interpretation of results, critical revision of the manuscript and final approval of the version to be published. **MN:** Data acquisition, data harmonisation, interpretation of results, critical revision of the manuscript and final approval of the version to be published. **FS:** Data acquisition, data harmonisation, interpretation of results, critical revision of the manuscript and final approval of the version to be published. **SvB:** Data harmonisation, critical revision of the manuscript, and redrafting and final approval of the version to be published. **SJ:** Data acquisition, data harmonisation, interpretation of results, critical revision of the manuscript and final approval of the version to be published. **VB:** Data acquisition, critical revision of the manuscript and final approval of the version to be published. **VP:** Data acquisition, data harmonisation, critical revision of the manuscript and final approval of the version to be published. **MK:** Design of the study, interpretation of results, critical revision of the manuscript and final approval of the version to be published. **LFLH:** Data acquisition, interpretation of results, critical revision of the manuscript and final approval of the version to be published. **PYA:** Concept and design of the study, data acquisition, data harmonisation, interpretation of results, critical revision of the manuscript and final approval of the version to be published. **NM:** Concept and design of the study, data acquisition, data harmonisation, interpretation of results, critical revision of the manuscript and final approval.

2. Acknowledgements

2.1. EXPRESS

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*Corresponding author

Email addresses: andrei.morgan@inserm.fr (Andrei S. Morgan PhD), jennifer.zeitlin@inserm.fr (Jennifer Zeitlin PhD), karin.kallen@med.lu.se (Karin Källén PhD), msn@leicester.ac.uk (Elizabeth S. Draper PhD), karel.marsal@med.lu.se (Karel Maršál PhD), mikael.norman@ki.se (Mikael Norman PhD), fredrik.serenius@kbh.uu.se (Fredrik Serenius PhD), stef.vanbuuren@tno.nl (Stef van Buuren PhD), sjj19@leicester.ac.uk (Samantha Johnson PhD), valerie.benhammou@inserm.fr (Valérie Benhammou PhD), veronique.pierrat@inserm.fr (Véronique Pierrat PhD), monique.kaminski@inserm.fr (Monique Kaminski MSc), laurencefoix@gmail.com (Laurence Foix L'Helias PhD), pierre-yves.ancel@inserm.fr (Pierre-Yves Ancel PhD), n.marlow@ucl.ac.uk (Neil Marlow FMedSci)

Solna, Stockholm; Gunnar Sjörs, MD, PhD, Department of Pediatrics, Uppsala University; Lennart Stigson, MD, Department of Pediatrics, Sahlgrenska University Hospital. Writing committee members: Vineta Fellman, MD, PhD, Department of Pediatrics, Clinical Sciences Lund, Lund University; Lena Hellström-Westas, MD, PhD, Department of Women's and Children's Health, Uppsala University; Mikael Norman, MD, PhD, Department of Pediatrics, Karolinska University Hospital, Huddinge and Department of Clinical Investigation, Intervention & Technology, Karolinska Institutet, Stockholm; Magnus Westgren, MD, PhD, Department of Obstetrics and Gynecology, Karolinska University Hospital Huddinge. Expert group members: Gerd Holmström, MD, PhD, Department of Oph- thalmology, Uppsala University; the late Ricardo Laurini, MD, PhD, Department of Pathology, Nordland Hospital, Bodö, Norway; Karin Stjernqvist, PhD, Department of Psychology, Lund University. Steering group and writing committee members: Karin Källén, PhD, Centre of Reproductive Epidemiology, Lund University; Hugo Lagercrantz, MD, PhD, Department of Women and Child Health, Karolinska Institute, Stockholm, Astrid Lindgren Children's Hospital, Stockholm; Karel Maršál, MD, PhD, Department of Obstetrics and Gynecology, Clinical Sciences Lund, Lund University; Fredrik Serenius, MD, PhD, Department of Clinical Sciences, Pediatrics, Umeå University; the late Margareta Wennergren, MD, PhD, Department of Obstetrics and Gynecology, Sahlgrenska University Hospital. Steering group members: the late Tore Nilstun, PhD, Department of Medical Ethics, Lund University; Petra Otterblad Olausson, PhD, Centre of Epidemiology, The National Board of Health and Welfare, Stockholm; Bo Strömberg, MD, PhD, Department of Pediatrics, Uppsala University.

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Independent members of EPICure studies steering committee: Peter Brocklehurst (chairman), Jane Abbott, Andrew Bush, Richard Cooke, Noreen Maconochie, Alison Matthews, David Matthews, Richard Morton, Maggie Redshaw, David Taylor, Nigel Turner, Diane Turner, Patrick Walsh.

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3. Ethical approvals

The EXPRESS study was approved by the Regional Research Ethics Board, Lund University, Lund, Sweden (reference 42/2004). The parents provided oral informed consent for perinatal data acquisition and written consent for examination of their children and data acquisition for the follow-up study. The

Regional Research Ethics Board of Lund University approved transfer of the anonymised data set used for this analysis (reference 2018/686).

The EPICure-2 study was approved by the East London Research Committee (ref 05/Q0605/107). Further approval was obtained (PIAG 3-07(f)/2005) to collect data without explicit consent. For surviving infants, consent was sought to use the data, maintain contact with the family, and to arrange for long term developmental assessment. The 3 year follow-up study was approved by the Northern and Yorkshire research ethics committee (ref 08/H0903/51). Permission for transfer of the anonymised data set used in this analysis was provided by the Data Owner and Study Sponsor.

The EPIPAGE-2 study was approved by the French National Data Protection Authority (CNIL, ref 911009) and by the relevant ethics committees: Consultative Committee on the Treatment of Data on Personal Health for Research Purposes (reference 10.626); Committee for the Protection of People Participating in Biomedical Research (reference CPP SC-2873). All data harmonisation and analyses were carried out in Paris, France.

4. Data sharing statement

The EXPRESS data are available for other researchers subject to approval from the relevant ethics committee and the EXPRESS Study Steering Committee. Researchers should contact the Chair of the Steering Committee (currently, Professor Mikael Norman) using contact details available online at `https://express-study.se/english/`.

The EPICure studies are subject to a data sharing policy that may be downloaded from `http://www.epicure.ac.uk`.

The EPIPAGE studies are subject to a data sharing policy that may be downloaded from `http://epipage2.inserm.fr/index.php/en/`.

Further information about all three cohorts is available on the RECAP Preterm platform at `https://platform.recap-preterm.eu/`. This platform contains detailed information, including data dictionaries, about a range of preterm birth cohorts carried out in Europe, and provides a mechanism for investigations to be facilitated.

5. Supplementary tables

Table S1: Variables from EXPRESS, EPICure-2 and EPIPAGE-2 cohorts harmonised for inclusion.

Variable	**EXPRESS**	**EPICure-2**	**EPIPAGE-2**	**Harmonised study version**
Gestational age (weeks)	1) ultrasound at 17-18 weeks GA; 2) last menstrual period; 3) other (unspecified).	1) Earliest ultrasound (normally performed at 11-12 weeks GA); 2) last menstrual period; 3) clinical estimation	Best obstetric estimate combining first trimester ultrasound (normally at 11-12 weeks GA) and last menstrual period.	Defined according to hierarchy shown for each cohort
Fetal sex	Male / Female	Male / Female	Male / Female	Male / Female
Maternal age (years)	(continuous)	(continuous)	(continuous)	(continuous)
Pre-pregnancy diabetes	Yes = Type I or II; No	Yes = Type I or II; No	Yes = Type I or II; No	Yes / No
Pre-pregnancy hypertension	Yes = hypertension diagnosed before pregnancy or at first booking ; No	Yes = Essential hypertension, on treatment at first booking ; No	Yes = persistent hypertension before the pregnancy ; No	Yes / No
Nulliparous	No previous deliveries of live births (at any GA) or still births ($\geq$ 28 weeks GA)	No previous deliveries ($\geq$ 24 weeks GA)	No previous deliveries ($\geq$ 22 weeks GA)	No previous deliveries (as defined by the cohorts)
Pre-eclampsia	Yes = BP $\geq$ 140/90 and proteinuria $\geq$ 0.3g/24 hours or 0.3g/l ; No	Yes / No	Yes = BP $\geq$ 140/90 and proteinuria $\geq$ 0.3g/24 hours ; No	Yes / No
Placental abruption	Yes / No	Yes / No	Yes / No	Yes / No
Labour onset	Spontaneous / induced / none	Spontaneous / induced / none	Spontaneous / induced / none	Spontaneous / Induced / None
Level of neonatal unit at delivery hospital	Levels 1 (basic neonatal care for term and near-term babies), 2 (County hospital with some neonatal care; most have 28 weeks' GA as a lower limit of care), and 3 (Regional university hospital with no lower GA limit)	Levels 1 (no onsite neonatal facilities other than for stabilisation), 2 (some neonatal care with a lower limit of 27 weeks' GA for singletons or 28 weeks' GA for multiples) and 3 (full intensive care provided to all babies with no lower GA limit)	Levels 1 (no onsite neonatal facilities), 2 (including 2a and 2b, providing stabilisation and/or short term neonatal care for late preterm and term babies only) and 3 (providing ongoing neonatal intensive care with no lower GA limit)	Levels 1, 2 and 3

(Continued on next page ...)

Variables from EXPRESS, EPICure-2 and EPIPAGE-2 cohorts harmonised for inclusion (continued).

Variable	**EXPRESS**	**EPICure-2**	**EPIPAGE-2**	**Harmonised study version**
Antenatal steroids (any)	Yes / No	Yes / No	Yes / No	Yes / No
Mode of delivery	Vaginal / Caesarean	Vaginal / Caesarean	Vaginal / Caesarean	Vaginal / Caesarean
Birth weight (g)	(continuous)	(continuous)	(continuous)	(continuous)
Congenital anomalies	Yes = Classified according to the WHO International Classification of Diseases, 10th revision (excluding: dislocation of the hip (Q65.0 Q65.5), preauricular tags (Q17.0), undescended testes (Q53.0–Q53.9), and patent ductus arteriosus (Q25.0)) / No	Yes = significant malformation noted at delivery / No	Yes = life-threatening malformation noted at delivery, retrospectively classified by committee of experts / No	Yes / No
Worst grade of IVH	Grades 1-4 according to the classification of Papile[1]	Grades 1-4 according to the classification of Papile[1]	Grades 1-4 according to the classification of Papile[1]	Grades 1-4 according to the classification of Papile[1]
Cystic PVL	Yes / No	Yes / No	Yes / No	Yes / No
PDA treated surgically	Yes / No	Yes / No	Yes / No	Yes / No
NEC treated surgically	Yes / No	Yes / No	Yes / No	Yes / No
BPD	None or mild; moderate; severe[2]	None or mild; moderate; severe[2]	None or mild; moderate; severe[2]	None or mild; moderate; severe[2]
Stage of ROP	Stages 1 to 5 according to the international classification[3]	Stages 1 to 5 according to the international classification[3]	Stages 1 to 5 according to the international classification[3]	Stages 1 to 5 according to the international classification[3]
Treated ROP	Yes / No	Yes / No	Yes / No	Yes / No
Blindness	Yes / No	Yes / No	Yes / No	Yes / No
Deafness	Yes / No	Yes / No	Yes / No	Yes / No
Functional motor level	None; mild (able to walk without an aid), moderate (able to walk with an aid) and severe (unable to walk, even with an aid).[4]	None; GMFCS levels 1 to 5, coded separately[5]	None; GMFCS levels coded as 1, 2, 3-4 combined, and 5[6]	no disability ; mild disability (GMFCS 1); moderate (GMFCS 2); severe (GMFCS 3-5)

GA: gestational age. BP: blood pressure. WHO: World Health Organisation. IVH: intraventricular haemorrhage.
PVL periventricular leukomalacia. PDA: patent ductus arteriosus. NEC: necrotising enterocolitis.
BPD: bronchopulmonary dysplasia. ROP: retinopathy of prematurity. GMFCS: Gross Motor Functional Classification System[7]

Table S2: STROBE checklist for "Outcomes of births between 22 and 26 weeks of gestation in national population-based cohorts from Sweden, England and France"

	Item No	Recommendation	Section (notes)
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Title ("population-based cohorts"; abstract ("We used harmonised data from three European cohorts to investigate timing of survival differences" with further details in methods section).
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract: Methods and Results sections.
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Background (paragraphs 1 and 2).
Objectives	3	State specific objectives, including any prespecified hypotheses	Background (second paragraph).
Methods			
Study design	4	Present key elements of study design early in the paper	Methods section.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods ("Data sources" section).
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods ("Data sources" and "Populations included" sections).
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods ("Data harmonisation" and "Outcomes" sections); supplementary table S1.
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.	Methods ("Data harmonisation" and "Outcomes" sections); supplementary table S1.
Bias	9	Describe any efforts to address potential sources of bias	Methods ("Populations included" and "Data harmonisation" sections); supplementary table S1.
Study size	10	Explain how the study size was arrived at	Methods ("Data sources" and "Populations included" sections).
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods ("Data sources").

Continued on next page...

Strobe checklist (continued)

	Item No	Recommendation	Section (notes)
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods ("Statistical analysis" section).
		(b) Describe any methods used to examine subgroups and interactions	Methods ("Statistical analysis" and "Sensitivity analyses" sections).
		(c) Explain how missing data were addressed	Methods ("Statistical analysis", second paragraph).
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	Methods ("Sensitivity analyses" section).
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results (paragraph 1) and figures 1to 4in the risk tables.
		(b) Give reasons for non-participation at each stage	Figures 1to 4
		(c) Consider use of a flow diagram	N/A
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results ("Maternal characteristics" and "Fetal characteristics" sections), and tables 1and 2and S4 to S5.
		(b) Indicate number of participants with missing data for each variable of interest	Results ("Neonatal outcomes at discharge" and "Post-discharge outcomes" sections), tables 4 and 5, and S6 to S9.
		(c) Summarise follow-up time (eg, average and total amount)	Figures 1 to 4.
Outcome data	15	Report numbers of outcome events or summary measures over time	Figures 1 to 4.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Main results (unadjusted and adjusted) are presented in tables 3 and S3, and S10 to S11; confounders are discussed in the methods ("Statistical analysis" section) and listed in the table captions.
		(b) Report category boundaries when continuous variables were categorized	Methods ("Statistical analysis" section) and tables 1 to 2 and S4 to S5.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done — eg analyses of subgroups and interactions, and sensitivity analyses	Results ("Sensitivity analyses" section) and tables S10 and S11.
Discussion			

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Strobe checklist (continued)

	Item No	Recommendation	Section (notes)
Key results	18	Summarise key results with reference to study objectives	Discussion (paragraph 1)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion ("Strengths and limitations" section).
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion ("Interpretation" section).
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion ("Generalisability" section).
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding section.

a Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article[8] (freely available on the Web sites of PLoS Medicine at `http://www.plosmedicine.org/`, Annals of Internal Medicine at `http://www.annals.org/`, and Epidemiology at `http://www.epidem.com/`). Information on the STROBE Initiative is available at `http://www.strobe-statement.org`.

Table S3: Chi-squared p-values testing scaled Schoenfeld residuals (to assess the proportional hazards assumption) for the EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts in comparison to EXPRESS (Sweden, 2004-07), along with residual tests for the overall model, from Cox regression for unadjusted and adjusted (for maternal age, parity, pre-existing diabetes and hypertension, pre-eclampsia, placental abruption, spontaneous labour, multiple preganancy, sex, and birth weight) models examining the mortality of babies born extremely preterm according to different baseline populations.

GA	Population	Unadjusted results			Adjusted results		
		EPICure-2	**EPIPAGE-2**	**Overall model**	**EPICure-2**	**EPIPAGE-2**	**Overall model**
22-23	Fetuses alive at maternal admission	0.004	0.469	<0.001	0.004	0.250	<0.001
	Live births	<0.001	0.702	<0.001	<0.001	0.982	<0.001
	Survived to 1 hour	0.060	0.381	0.151	0.005	0.063	0.085
	Survived to 1 day	0.903	0.433	0.725	0.990	0.486	0.511
	Survived to 7 days	0.557	0.147	0.178	0.561	0.118	0.356
	Survived to 28 days	0.229	0.258	0.375	>0.999	>0.999	>0.999
24	Fetuses alive at maternal admission	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Live births	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Survived to 1 hour	0.036	0.010	0.036	0.075	0.019	0.206
	Survived to 1 day	0.022	0.013	0.036	0.034	0.022	0.029
	Survived to 7 days	0.055	0.022	0.066	0.194	0.089	0.503
	Survived to 28 days	0.461	0.015	0.029	0.416	0.012	0.423
25	Fetuses alive at maternal admission	0.757	0.834	0.951	0.522	0.446	0.025
	Live births	0.793	0.967	0.890	0.921	0.708	0.425
	Survived to 1 hour	0.637	0.767	0.888	0.818	0.943	0.197
	Survived to 1 day	0.484	0.725	0.744	0.721	0.976	0.188
	Survived to 7 days	0.398	0.056	0.077	0.363	0.075	0.101
	Survived to 28 days	0.022	0.030	0.053	0.016	0.030	0.263
26	Fetuses alive at maternal admission	0.822	0.671	0.898	0.510	0.444	0.112
	Live births	0.539	0.490	0.783	0.278	0.268	0.200
	Survived to 1 hour	0.747	0.855	0.943	0.494	0.593	0.123
	Survived to 1 day	0.029	0.132	0.088	0.019	0.061	0.128
	Survived to 7 days	0.455	0.478	0.741	0.235	0.327	0.548
	Survived to 28 days	0.654	0.324	0.152	>0.999	>0.999	>0.999

Notes: GA: gestational age at delivery.

Table S4: Baseline data for 22-23 and 24 week gestational age fetuses alive at maternal admission to hospital from the EXPRESS (Sweden, 2004-06), EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts.

Variable	22-23 weeks of gestational age							24 weeks of gestational age						
Levels	EXPRESS		EPICure-2		EPIPAGE-2		p-value	EXPRESS		EPICure-2		EPIPAGE-2		p-value
	n	%	n	%	n	%		n	%	n	%	n	%	
Level of neonatal care at delivery hospital														
1	9	4.3	90	13.6	45	12.3	<0.001	2	1.4	51	10.5	16	6.5	<0.001
2	70	33.5	266	40.1	156	42.6		11	7.6	154	31.7	48	19.5	
3	130	62.2	308	46.4	165	45.1		131	91	281	57.8	182	74.0	
Missing	*0*	–	*11*	–	*0*	–		*2*	–	*7*	–	*0*	–	
Exposure to antenatal steroids														
No	80	39.8	421	62.7	327	95.9	<0.001	7	5.0	77	15.7	121	52.2	<0.001
Yes	121	60.2	250	37.3	14	4.1		134	95.0	412	84.3	111	47.8	
Missing	*8*	–	*4*	–	*25*	–		*5*	–	*4*	–	*14*	–	
Placental abruption														
No	183	91.0	629	93.6	347	97.7	0.002	124	93.2	463	94.3	235	97.5	0.1
Yes	18	9.0	43	6.4	8	2.3		9	6.8	28	5.7	6	2.5	
Missing	*8*	–	*3*	–	*11*	–		*13*	–	*2*	–	*5*	–	
Multiple birth														
No	161	77	485	71.9	249	68.0	0.069	114	78.1	366	74.2	177	72.0	0.406
Yes	48	23	190	28.1	117	32.0		32	21.9	127	25.8	69	28.0	
Delivery type														
Vaginal	189	90.4	661	98.1	343	96.9	<0.001	79	54.1	426	86.4	208	88.9	<0.001
Caesarean	20	9.6	13	1.9	11	3.1		67	45.9	67	13.6	26	11.1	
Missing	*0*	–	*1*	–	*12*	–		*0*	–	*0*	–	*12*	–	
Sex														
Male	113	54.3	374	55.7	208	57.0	0.823	78	53.4	253	51.3	127	52.0	0.903
Female	95	45.7	297	44.3	157	43.0		68	46.6	240	48.7	117	48.0	
Missing	*1*	–	*4*	–	*1*	–		*0*	–	*0*	–	*2*	–	
Birth weight (g)														
<500	69	34.3	214	32.6	121	35.8	0.596	11	7.6	23	4.7	8	3.4	0.162
≥=500	132	65.7	442	67.4	217	64.2		133	92.4	470	95.3	230	96.6	
Missing	*8*	–	*19*	–	*28*	–		*2*	–	*0*	–	*8*	–	
Congenital anomalies														
No	200	95.7	644	98.5	363	99.5	0.003	131	89.7	462	96.9	245	99.6	<0.001
Yes	9	4.3	10	1.5	2	0.5		15	10.3	15	3.1	1	0.4	
Missing	*0*	–	*21*	–	*1*	–		*0*	–	*16*	–	*0*	–	

Notes: g: grams.

Table S5: Baseline data for 25 and 26 week gestational age fetuses alive at maternal admission to hospital from the EXPRESS (Sweden, 2004-06), EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts.

Variable	25 weeks of gestational age							26 weeks of gestational age						
Levels	EXPRESS		EPICure-2		EPIPAGE-2		p-value	EXPRESS		EPICure-2		EPIPAGE-2		p-value
	n	%	n	%	n	%		n	%	n	%	n	%	
Level of neonatal care at delivery hospital														
1	6	3.0	34	6.3	12	3.7	<0.001	3	1.4	42	7.2	14	3.3	<0.001
2	27	13.5	148	27.3	41	12.6		44	21.1	189	32.3	45	10.7	
3	167	83.5	360	66.4	272	83.7		162	77.5	355	60.6	363	86.0	
Missing	*5*	–	*6*	–	*0*	–		*0*	–	*8*	–	*0*	–	
Antenatal steroids														
No	24	12.1	67	12.3	80	25.3	<0.001	14	7.1	84	14.3	82	19.7	<0.001
Yes	174	87.9	477	87.7	236	74.7		183	92.9	502	85.7	334	80.3	
Missing	*7*	–	*4*	–	*9*	–		*12*	–	*8*	–	*6*	–	
Placental abruption														
No	169	86.7	506	93.0	308	96.2	<0.001	165	85.5	539	91.2	388	93.7	0.004
Yes	26	13.3	38	7.0	12	3.8		28	14.5	52	8.8	26	6.3	
Missing	*10*	–	*4*	–	*5*	–		*16*	–	*3*	–	*8*	–	
Multiple birth														
No	167	81.5	435	79.4	202	62.2	<0.001	158	75.6	435	73.2	307	72.7	0.735
Yes	38	18.5	113	20.6	123	37.8		51	24.4	159	26.8	115	27.3	
Delivery type														
Vaginal	78	38.0	377	69.2	211	66.4	<0.001	67	32.1	336	56.7	171	40.8	<0.001
Caesarean	127	62.0	168	30.8	107	33.6		142	67.9	257	43.3	248	59.2	
Missing	*0*	–	*3*	–	*7*	–		*0*	–	*1*	–	*3*	–	
Sex														
Male	119	58	295	53.8	181	55.7	0.571	110	52.6	296	49.8	217	51.4	0.753
Female	86	42	253	46.2	144	44.3		99	47.4	298	50.2	205	48.6	
Missing	*0*	–	*0*	–	*0*	–		*0*	–	*0*	–	*0*	–	
Birth weight (g)														
<500g	8	3.9	13	2.4	4	1.2	0.138	3	1.4	10	1.7	9	2.1	0.791
≥500g	197	96.1	535	97.6	320	98.8		206	98.6	584	98.3	413	97.9	
Missing	*0*	–	*0*	–	*1*	–		*0*	–	*0*	–	*0*	–	
Congenital anomalies														
No	175	85.4	520	98.3	314	96.9	<0.001	184	88.0	564	97.2	413	97.9	<0.001
Yes	30	14.6	9	1.7	10	3.1		25	12.0	16	2.8	9	2.1	
Missing	*0*	–	*19*	–	*1*	–		*0*	–	*14*	–	*0*	–	

Notes: g: grams.

Table S6: Data for 22-23 and 24 week gestational age babies from the EXPRESS (Sweden, 2004-06), EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts who were discharged alive from hospital.

Variable	22-23 weeks of gestational age							24 weeks of gestational age						
Levels	EXPRESS		EPICure-2		EPIPAGE-2		p-value	EXPRESS		EPICure-2		EPIPAGE-2		p-value
	n	%	n	%	n	%		n	%	n	%	n	%	
Sex														
Male	27	46.6	37	53.6	1	100.0	0.448	51	53.7	82	46.1	29	50.0	0.48
Female	31	53.4	32	46.4	0	0.0		44	46.3	96	53.9	29	50.0	
Birth weight (g)														
<500g	6	10.3	3	4.3	0	0.0	0.405	5	5.3	1	0.6	1	1.7	0.036
≥500g	52	89.7	66	95.7	1	100.0		90	94.7	177	99.4	57	98.3	
Congenital anomalies														
No	52	89.7	66	98.5	1	100.0	0.095	86	90.5	170	98.8	58	100.0	<0.001
Yes	6	10.3	1	1.5	0	0.0		9	9.5	2	1.2	0	0.0	
Missing	*0*	–	*2*	–	*0*	–		*0*	–	*6*	–	*0*	–	
Highest grade of IVH														
0	31	53.4	25	36.8	1	100.0	0.244	60	63.2	66	37.3	27	46.6	<0.001
1	9	15.5	16	23.5	0	0.0		18	18.9	29	16.4	7	12.1	
2	7	12.1	18	26.5	0	0.0		8	8.4	44	24.9	17	29.3	
3	6	10.3	2	2.9	0	0.0		3	3.2	13	7.3	5	8.6	
4	5	8.6	7	10.3	0	0.0		6	6.3	25	14.1	2	3.4	
Missing	*0*	–	*1*	–	*0*	–		*0*	–	*1*	–	*0*	–	
Cystic PVL														
No	53	91.4	64	94.1	1	100.0	0.805	90	94.7	168	94.9	57	98.3	0.523
Yes	5	8.6	4	5.9	0	0.0		5	5.3	9	5.1	1	1.7	
Missing	*0*	–	*1*	–	*0*	–		*0*	–	*1*	–	*0*	–	
PDA treated surgically														
No	28	48.3	43	62.3	0	0.0	0.152	50	52.6	137	77.0	35	62.5	<0.001
Yes	30	51.7	26	37.7	1	100.0		45	47.4	41	23.0	21	37.5	
Missing	*0*	–	*0*	–	*0*	–		*0*	–	*0*	–	*2*	–	
NEC treated surgically														
No	56	96.6	64	92.8	0	0.0	<0.001	88	95.7	158	88.8	55	94.8	0.096
Yes	2	3.4	5	7.2	1	100.0		4	4.3	20	11.2	3	5.2	
Missing	*0*	–	*0*	–	*0*	–		*3*	–	*0*	–	*0*	–	
Bronchopulmonary dysplasia														
None/mild	7	13.0	9	13.0	0	0.0	<0.001	19	21.6	32	18.0	23	46.0	<0.001
Moderate	32	59.3	16	23.2	0	0.0		42	47.7	51	28.7	8	16.0	
Severe	15	27.8	44	63.8	1	100.0		27	30.7	95	53.4	19	38.0	
Missing	*4*	–	*0*	–	*0*	–		*7*	–	*0*	–	*8*	–	
Treated ROP														
No	13	28.3	32	59.3	1	100.0	0.004	24	43.6	84	63.6	32	82.1	<0.001
Yes	33	71.7	22	40.7	0	0.0		31	56.4	48	36.4	7	17.9	
Missing	*12*	–	*15*	–	*0*	–		*40*	–	*46*	–	*19*	–	
ROP Stage														
0	5	8.6	14	20.6	0	0.0	0.145	14	14.9	45	25.4	12	31.6	0.092
1	5	8.6	10	14.7	0	0.0		10	10.6	27	15.3	10	26.3	
2	11	19.0	15	22.1	1	100.0		25	26.6	42	23.7	7	18.4	
3	35	60.3	27	39.7	0	0.0		43	45.7	62	35.0	9	23.7	
4	0	0.0	2	2.9	0	0.0		1	1.1	0	0.0	0	0.0	
5	2	3.4	0	0.0	0	0.0		1	1.1	1	0.6	0	0.0	
Missing	*0*	–	*1*	–	*0*	–		*1*	–	*1*	–	*20*	–	
Total number of neonatal morbidities														
0	10	17.2	16	23.2	0	0.0	0.338	31	32.6	52	29.2	28	48.3	0.002
1	30	51.7	24	34.8	0	0.0		41	43.2	55	30.9	22	37.9	
2	14	24.1	20	29.0	1	100.0		20	21.1	46	25.8	7	12.1	
3	4	6.9	9	13.0	0	0.0		3	3.2	22	12.4	1	1.7	
4	0	0.0	0	0.0	0	0.0		0	0.0	3	1.7	0	0.0	
Missing	0	–	0	–	0	–		0	–	0	–	0	–	

Notes: IVH: intraventricular haemorrhage; PVL: periventricular leukomalacia; PDA: patent ductus arteriosus; NEC: necrotising enterocolitis; ROP: retinopathy of prematurity. Total neonatal morbidities: IVH ≥ grade III, PVL, surgically treated NEC, ROP ≥ stage 3, severe bronchopulmonary dysplasia.

Table S7: Data for 25 and 26 week gestational age babies from the EXPRESS (Sweden, 2004-06), EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts who were discharged alive.

Variable		25 weeks of gestational age							26 weeks of gestational age						
	Levels	EXPRESS		EPICure-2		EPIPAGE-2		p-value	EXPRESS		EPICure-2		EPIPAGE-2		p-value
		n	%	n	%	n	%		n	%	n	%	n	%	
Sex															
	Male	98	59.8	167	48.4	94	51.9	0.057	94	52.2	219	48.9	156	50.2	0.748
	Female	66	40.2	178	51.6	87	48.1		86	47.8	229	51.1	155	49.8	
Birth weight (g)															
	<500g	4	2.4	3	0.9	1	0.6	0.204	3	1.7	5	1.1	2	0.6	0.561
	≥500g	160	97.6	342	99.1	180	99.4		177	98.3	443	98.9	309	99.4	
Congenital anomalies															
	No	145	88.4	335	99.1	179	98.9	<0.001	159	88.3	433	98.9	307	98.7	<0.001
	Yes	19	11.6	3	0.9	2	1.1		21	11.7	5	1.1	4	1.3	
	Missing	*0*	–	*7*	–	*0*	–		*0*	–	*10*	–	*0*	–	
Highest grade of IVH															
	0	98	59.8	164	47.7	78	43.1	<0.001	121	68.8	235	52.7	180	57.9	<0.001
	1	30	18.3	59	17.2	30	16.6		32	18.2	66	14.8	56	18.0	
	2	16	9.8	46	13.4	59	32.6		14	8.0	80	17.9	50	16.1	
	3	13	7.9	21	6.1	7	3.9		4	2.3	18	4.0	17	5.5	
	4	7	4.3	54	15.7	7	3.9		5	2.8	47	10.5	8	2.6	
	Missing	*0*	–	*1*	–	*0*	–		*4*	–	*2*	–	*0*	–	
Cystic PVL															
	No	155	94.5	326	94.8	177	97.8	0.222	171	95.0	418	93.7	303	97.4	0.063
	Yes	9	5.5	18	5.2	4	2.2		9	5.0	28	6.3	8	2.6	
	Missing	*0*	–	*1*	–	*0*	–		*0*	–	*2*	–	*0*	–	
PDA treated surgically															
	No	124	75.6	284	82.8	120	67.4	<0.001	160	88.9	403	91.0	251	83.9	0.014
	Yes	40	24.4	59	17.2	58	32.6		20	11.1	40	9.0	48	16.1	
	Missing	*0*	–	*2*	–	*3*	–		*0*	–	*5*	–	*12*	–	
NEC treated surgically															
	No	154	95.1	320	92.8	173	95.6	0.352	178	99.4	419	93.5	298	95.8	0.006
	Yes	8	4.9	25	7.2	8	4.4		1	0.6	29	6.5	13	4.2	
	Missing	*2*	–	*0*	–	*0*	–		*1*	–	*0*	–	*0*	–	
Bronchopulmonary dysplasia															
	None/mild	47	31.3	111	32.2	95	58.6	<0.001	69	42.9	171	38.3	186	64.8	<0.001
	Moderate	59	39.3	99	28.7	20	12.3		66	41.0	125	28.0	36	12.5	
	Severe	44	29.3	135	39.1	47	29.0		26	16.1	151	33.8	65	22.6	
	Missing	*14*	–	*0*	–	*19*	–		*19*	–	*1*	–	*24*	–	
Treated ROP															
	No	50	64.1	161	73.9	97	90.7	<0.001	37	64.9	197	83.5	200	98.0	<0.001
	Yes	28	35.9	57	26.1	10	9.3		20	35.1	39	16.5	4	2.0	
	Missing	*86*	–	*127*	–	*74*	–		*123*	–	*212*	–	*107*	–	
ROP stage															
	0	39	23.8	126	36.6	53	48.6	<0.001	79	44.9	208	46.8	121	58.2	<0.001
	1	33	20.1	61	17.7	20	18.3		27	15.3	100	22.5	47	22.6	
	2	39	23.8	84	24.4	22	20.2		37	21.0	88	19.8	35	16.8	
	3	51	31.1	73	21.2	13	11.9		33	18.8	47	10.6	5	2.4	
	4	2	1.2	0	0.0	1	0.9		0	0.0	1	0.2	0	0.0	
	5	0	0.0	0	0.0	0	0.0		0	0.0	0	0.0	0	0.0	
	Missing	*0*	–	*1*	–	*72*	–		*4*	–	*4*	–	*103*	–	
Total number of neonatal morbidities															
	0	74	45.1	126	36.5	111	61.3	<0.001	116	64.4	216	48.2	209	67.2	<0.001
	1	56	34.1	139	40.3	55	30.4		53	29.4	155	34.6	88	28.3	
	2	26	15.9	56	16.2	13	7.2		8	4.4	66	14.7	14	4.5	
	3	6	3.7	21	6.1	2	1.1		3	1.7	10	2.2	0	0.0	
	4	2	1.2	3	0.9	0	0.0		0	0.0	1	0.2	0	0.0	
	Missing	0	–	0	–	0	–		0	–	0	–	0	–	

Notes: IVH: intraventricular haemorrhage; PVL: periventricular leukomalacia; PDA: patent ductus arteriosus; NEC: necrotising enterocolitis; ROP: retinopathy of prematurity. Total neonatal morbidities: IVH ≥ grade III, PVL, surgically treated NEC, ROP ≥ stage 3, severe bronchopulmonary dysplasia.

Table S8: Data for 22-23 and 24 week gestational age 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	22-23 weeks of gestational age							24 weeks of gestational age						
Levels	EXPRESS		EPICure-2		EPIPAGE-2		p-value	EXPRESS		EPICure-2		EPIPAGE-2		p-value
	n	%	n	%	n	%		n	%	n	%	n	%	
Survived to follow-up *														
Yes	55	96.5	66	95.7	1	100.0	0.952	91	97.8	177	99.4	58	100.0	0.308
No	2	3.5	3	4.3	0	0.0		2	2.2	1	0.6	0	0.0	
Blind														
No	51	98.1	37	97.4	1	100.0	0.964	84	97.7	97	99.0	49	100.0	0.491
Yes	1	1.9	1	2.6	0	0.0		2	2.3	1	1.0	0	0.0	
Missing	*3*	–	*28*	–	*0*	–		*5*	–	*79*	–	*9*	–	
Deaf														
No	49	100	37	97.4	1	100.0	0.514	81	98.8	98	100.0	49	100.0	0.406
Yes	0	0.0	1	2.6	0	0.0		1	1.2	0	0.0	0	0.0	
Missing	*6*	–	*28*	–	*0*	–		*9*	–	*79*	–	*9*	–	
Functional motor impairment level (GMFCS)														
None	47	90.4	32	65.3	1	100	0.037	80	93.0	103	75.2	45	90.0	0.006
Mild (GMFCS 1)	1	1.9	10	20.4	0	0.0		2	2.3	22	16.1	3	6.0	
Moderate (GMFCS 2)	3	5.8	2	4.1	0	0.0		3	3.5	5	3.6	2	4.0	
Severe (GMFCS 3-5)	1	1.9	5	10.2	0	0.0		1	1.2	7	5.1	0	0.0	
Missing	*3*	–	*17*	–	*0*	–		*5*	–	*40*	–	*8*	–	

Notes: GMFCS: Gross Motor Functional Classification System.
* Three children from EXPRESS had emigrated or had a protected identity at 2.5 years of age, hence survival information were not available; they have been excluded from this table.

Table S9: Data for 25 and 26 week gestational age 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		25 weeks of gestational age							26 weeks of gestational age						
	Levels	EXPRESS		EPICure-2		EPIPAGE-2		p-value	EXPRESS		EPICure-2		EPIPAGE-2		p-value
		n	%	n	%	n	%		n	%	n	%	n	%	
Survived to follow-up *															
	Yes	161	98.8	340	98.6	180	99.4	0.657	174	97.2	446	99.6	305	98.1	0.046
	No	2	1.2	5	1.4	1	0.6		5	2.8	2	0.4	6	1.9	
Blind															
	No	148	99.3	187	99.5	128	99.2	0.964	168	100.0	248	98.8	240	99.6	0.27
	Yes	1	0.7	1	0.5	1	0.8		0	0.0	3	1.2	1	0.4	
	Missing	*12*	–	*152*	–	*51*	–		*6*	–	*195*	–	*64*	–	
Deaf															
	No	147	100.0	188	100.0	138	100.0	N/A	165	100.0	251	100.0	253	100.0	N/A
	Yes	0	0.0	0	0.0	0	0.0		0	0.0	0	0.0	0	0.0	
	Missing	*14*	–	*152*	–	*42*	–		*9*	–	*195*	–	*52*	–	
Functional motor impairment level (GMFCS)															
	None	139	93.3	191	77.6	126	89.4	0.002	157	93.5	265	83.1	246	95.7	<0.001
	Mild (GMFCS 1)	5	3.4	30	12.2	8	5.7		5	3.0	28	8.8	0	0.0	
	Moderate (GMFCS 2)	3	2.0	11	4.5	3	2.1		4	2.4	9	2.8	7	2.7	
	Severe (GMFCS 3-5)	2	1.3	14	5.7	4	2.8		2	1.2	17	5.3	4	1.6	
	Missing	*12*	–	*94*	–	*39*	–		*6*	–	*127*	–	*48*	–	

Notes: GMFCS: Gross Motor Functional Classification System; N/A: not applicable.

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

Table S10: Hazard ratios for mortality of singleton babies born extremely preterm in the EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts in comparison to 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, sex, and birth weight.

GA	Population	Unadjusted results					Adjusted results				
		n	EPICure-2		EPIPAGE-2		n	EPICure-2		EPIPAGE-2	
			HR	(95% CI)	HR	(95% CI)		HR	(95% CI)	HR	(95% CI)
22-23	Fetuses alive at maternal admission	895	1.60	(1.29 – 1.97)	3.85	(3.05 – 4.86)	824	1.56	(1.24 – 1.97)	4.15	(3.20 – 5.38)
	Live births	559	2.10	(1.60 – 2.76)	4.72	(3.41 – 6.55)	530	2.05	(1.52 – 2.76)	5.51	(3.84 – 7.92)
	Survived to 1 hour	395	2.82	(1.99 – 3.99)	6.39	(4.13 – 9.89)	377	2.63	(1.82 – 3.81)	7.08	(4.36 – 11.49)
	Survived to 1 day	202	3.70	(2.17 – 6.33)	5.03	(1.84 – 13.77)	199	3.66	(2.10 – 6.36)	4.83	(1.55 – 14.99)
	Survived to 7 days	152	4.57	(2.15 – 9.71)	7.04	(1.86 – 26.64)	150	4.75	(2.17 – 10.39)	4.89	(0.96 – 24.91)
	Survived to 28 days	118	9.03	(2.10 – 38.79)	14.31	(1.29 – 158.16)	117	12.52	(2.58 – 60.82)	12.19	(0.84 – 176.80)
24	Fetuses alive at maternal admission	657	2.42	(1.72 – 3.41)	4.49	(3.13 – 6.44)	626	2.24	(1.56 – 3.22)	4.26	(2.91 – 6.24)
	Live births	569	2.17	(1.52 – 3.09)	3.76	(2.56 – 5.52)	546	2.06	(1.41 – 3.01)	3.64	(2.42 – 5.48)
	Survived to 1 hour	503	2.47	(1.66 – 3.66)	3.17	(2.03 – 4.94)	484	2.38	(1.57 – 3.62)	2.94	(1.83 – 4.71)
	Survived to 1 day	409	2.25	(1.42 – 3.56)	2.58	(1.50 – 4.44)	394	2.17	(1.33 – 3.51)	2.29	(1.29 – 4.07)
	Survived to 7 days	367	2.75	(1.59 – 4.77)	2.26	(1.14 – 4.48)	354	2.89	(1.61 – 5.19)	1.96	(0.93 – 4.10)
	Survived to 28 days	296	2.65	(1.18 – 5.97)	1.76	(0.59 – 5.23)	287	2.61	(1.11 – 6.11)	1.84	(0.61 – 5.58)
25	Fetuses alive at maternal admission	804	2.05	(1.40 – 2.99)	2.79	(1.86 – 4.17)	770	1.97	(1.31 – 2.94)	2.68	(1.74 – 4.12)
	Live births	760	1.90	(1.27 – 2.85)	2.64	(1.72 – 4.05)	729	1.85	(1.20 – 2.84)	2.56	(1.62 – 4.04)
	Survived to 1 hour	736	1.89	(1.23 – 2.89)	2.75	(1.75 – 4.32)	707	1.85	(1.17 – 2.91)	2.71	(1.68 – 4.39)
	Survived to 1 day	694	1.80	(1.13 – 2.87)	2.62	(1.59 – 4.30)	667	1.86	(1.13 – 3.07)	2.74	(1.61 – 4.67)
	Survived to 7 days	633	2.27	(1.22 – 4.23)	3.01	(1.55 – 5.84)	610	2.18	(1.12 – 4.24)	3.32	(1.65 – 6.72)
	Survived to 28 days	571	1.60	(0.69 – 3.70)	1.84	(0.71 – 4.76)	550	1.82	(0.70 – 4.73)	2.68	(0.94 – 7.66)
26	Fetuses alive at maternal admission	900	1.89	(1.19 – 2.99)	2.15	(1.34 – 3.43)	856	1.95	(1.21 – 3.16)	2.18	(1.33 – 3.56)
	Live births	879	1.88	(1.16 – 3.04)	2.15	(1.32 – 3.53)	835	1.98	(1.19 – 3.27)	2.16	(1.29 – 3.62)
	Survived to 1 hour	866	1.77	(1.09 – 2.87)	1.97	(1.19 – 3.23)	823	1.90	(1.14 – 3.15)	1.95	(1.16 – 3.29)
	Survived to 1 day	824	1.51	(0.89 – 2.58)	1.87	(1.09 – 3.23)	784	1.63	(0.93 – 2.87)	1.91	(1.07 – 3.38)
	Survived to 7 days	768	1.72	(0.87 – 3.43)	1.66	(0.81 – 3.43)	729	1.37	(0.67 – 2.79)	1.18	(0.56 – 2.48)
	Survived to 28 days	717	1.85	(0.63 – 5.48)	1.23	(0.37 – 4.07)	679	1.30	(0.42 – 4.06)	0.66	(0.18 – 2.43)

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

Table S11: Mortality of singleton babies born extremely premature according to different baseline populations: chi-squared p-values testing scaled Schoenfeld residuals (to assess the proportional hazards assumption) for the EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts in comparison to EXPRESS (Sweden, 2004-07), along with residual tests for the overall model. Obtained from Cox regression unadjusted and adjusted (for maternal age, parity, pre-existing diabetes and hypertension, pre-eclampsia, placental abruption, spontaneous labour, sex, and birth weight) models .

GA	Population	Unadjusted results			Adjusted results		
		EPICure-2	**EPIPAGE-2**	**Overall model**	**EPICure-2**	**EPIPAGE-2**	**Overall model**
22-23	Fetuses alive at maternal admission	<0.001	0.848	<0.001	0.001	0.752	<0.001
	Live births	0.002	0.857	<0.001	0.001	0.784	0.009
	Survived to 1 hour	0.039	0.978	0.022	0.002	0.185	0.102
	Survived to 1 day	0.663	0.457	0.529	0.529	0.539	0.253
	Survived to 7 days	0.895	0.165	0.262	0.868	0.111	0.601
	Survived to 28 days	0.338	0.241	0.464	>0.999	>0.999	>0.999
24	Fetuses alive at maternal admission	0.004	<0.001	0.001	0.008	<0.001	<0.001
	Live births	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
	Survived to 1 hour	0.071	0.019	0.064	0.127	0.028	0.490
	Survived to 1 day	0.015	0.011	0.027	0.035	0.029	0.479
	Survived to 7 days	0.434	0.131	0.301	0.997	0.455	0.946
	Survived to 28 days	0.490	0.011	0.020	0.441	0.010	0.482
25	Fetuses alive at maternal admission	0.779	0.988	0.895	0.392	0.392	0.089
	Live births	0.847	0.937	0.976	0.841	0.579	0.691
	Survived to 1 hour	0.459	0.475	0.741	0.773	0.916	0.243
	Survived to 1 day	0.394	0.565	0.691	0.729	0.993	0.282
	Survived to 7 days	0.664	0.242	0.377	0.600	0.278	0.493
	Survived to 28 days	0.120	0.615	0.221	0.108	0.567	0.582
26	Fetuses alive at maternal admission	0.998	0.775	0.886	0.675	0.463	0.078
	Live births	0.888	0.634	0.818	0.526	0.304	0.111
	Survived to 1 hour	0.995	0.994	>0.999	0.689	0.624	0.086
	Survived to 1 day	0.124	0.303	0.296	0.078	0.126	0.132
	Survived to 7 days	0.424	0.717	0.671	>0.999	>0.999	>0.999
	Survived to 28 days	0.770	0.363	0.236	>0.999	>0.999	>0.999

Notes: GA: gestational age (weeks) at delivery.

6. Supplementary figures

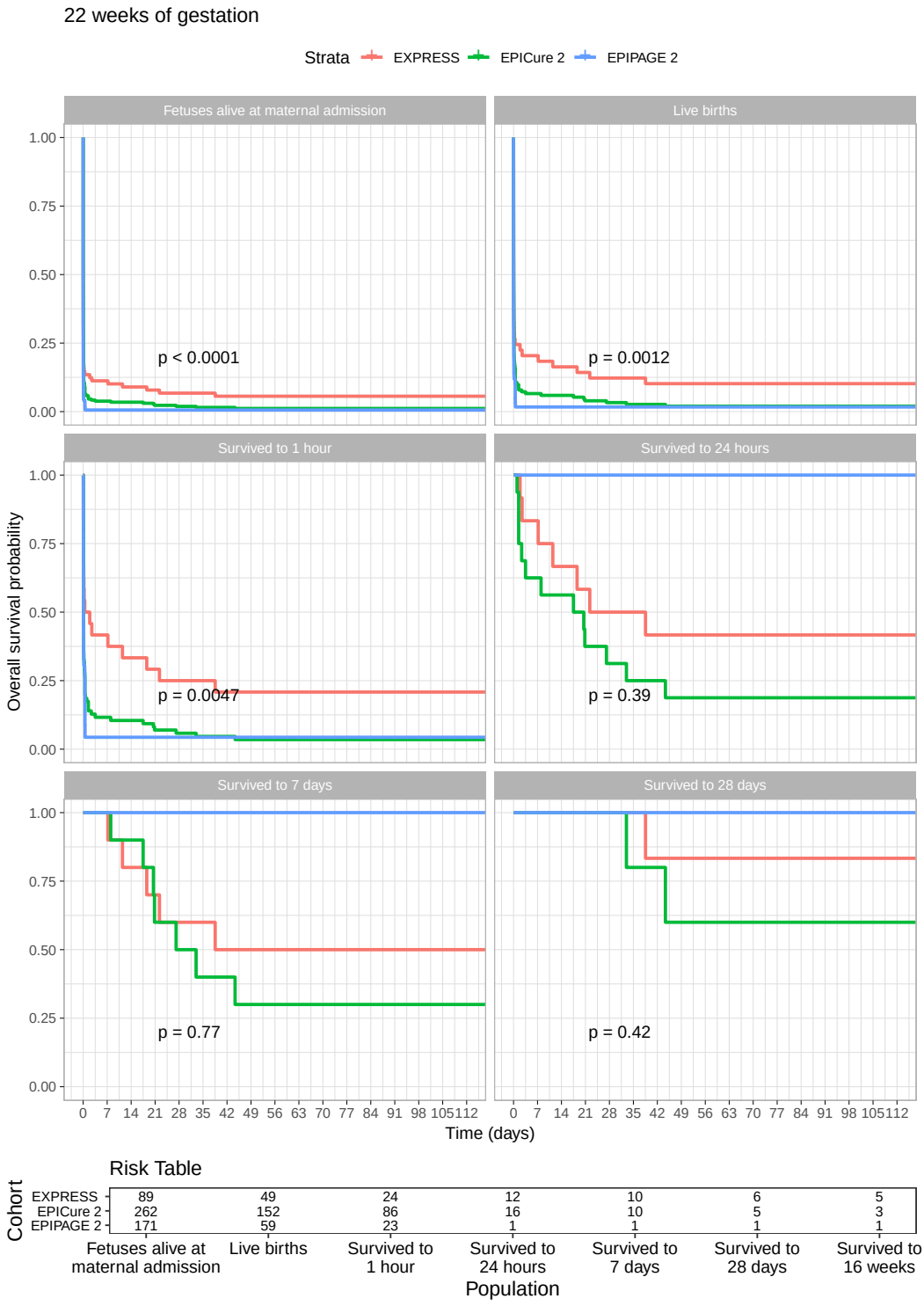

Figure 1: Survival curves for the EXPRESS (Sweden, 2004-07), EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts for fetuses born at 22 completed weeks of gestational age.

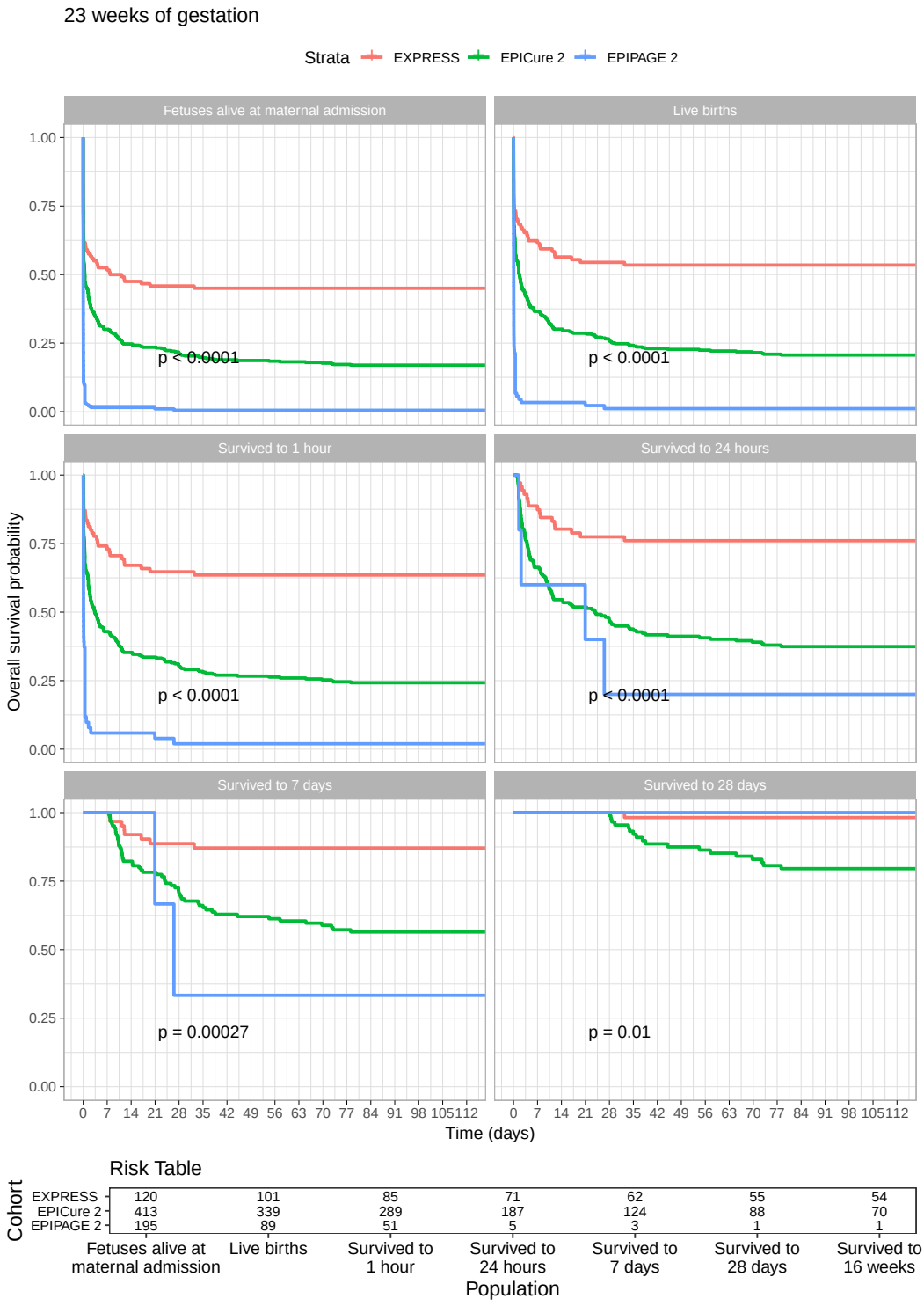

Figure 2: Survival curves for the EXPRESS (Sweden, 2004-07), EPICure-2 (England, 2006) and EPIPAGE-2 (France, 2011) cohorts for fetuses born at 23 completed weeks of gestational age.

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