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Survival and neurodevelopmental impairment of outborn preterm infants at 5.5 years of age: an EPIPAGE-2 prospective, matched study using multiple imputation

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ABSTRACT

Objective To determine whether birth outside a level-3 centre (outborn) is associated with a difference in the combined outcome of mortality or moderate-to-severe neurological impairment at 5.5 years of age compared with birth in a level-3 centre (inborn) when antenatal steroids and gestational age (GA) are accounted for.

Design Individual matched study nested within a prospective cohort. Each outborn infant was matched using GA and antenatal steroids with a maximum of four inborns. Conditional logistic regression was used to calculate ORs before being adjusted using maternal and birth characteristics. Analyses were carried out after multiple imputation for missing data.

Setting EPIPAGE-2 French national prospective cohort including births up to 34 weeks GA inclusive.

Patients Outborn and inborn control infants selected between 24 and 31 weeks GA were followed in the neonatal period and to 2 and 5.5 years. 3335 infants were eligible of whom all 498 outborns and 1235 inborn infants were included—equivalent to 2.5 inborns for each outborn.

Main outcome measure Survival without moderate-to-severe neurodevelopmental impairment at 5.5 years.

Results Chorioamnionitis, pre-eclampsia, caesarian birth and small-for-dates were more frequent among inborns, and spontaneous labour and antepartum haemorrhage among outborns. There was no difference in the main outcome measure at 5.5 years of age (adjusted OR 1.09, 95% CI 0.82 to 1.44); sensitivity analyses suggested improved outcomes at lower GAs for inborns.

Conclusion In this GA and steroid matched cohort, there was no difference in survival without moderate-to-severe neurodevelopmental impairment to 5.5 years of age between inborn and outborn very preterm children. This suggests steroids might be important in determining outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Excess mortality and/or neurological complications have been demonstrated in preterm infants born outside neonatal intensive care units compared with inborns in many countries.
⇒ Pre-eclampsia, premature rupture of membranes and small for gestational age are frequent in inborns whereas spontaneous birth and placental abruption are frequent in outborns.
⇒ Administration of antenatal steroids is lower in outborn than inborn pregnancies, and is independently associated with worse outcomes.

WHAT THIS STUDY ADDS

⇒ There were no differences in survival to 5.5 years without moderate/severe neurodevelopmental impairment between inborns and outborns when gestational age and antenatal steroids were accounted for.
⇒ There were improved outcomes at 5.5 years with inborn delivery for births at 24–27 weeks of gestation, but not below 24 weeks.
⇒ There were no differences in outcomes at 2 years of age or at hospital discharge–other than for necrotising enterocolitis, which was more frequent among outborns.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Improved protocols should be implemented to enhance antenatal transfer of women delivering at extremely preterm gestations.
⇒ Administration of antenatal steroids to women presenting to non-level 3 units who risk premature delivery should be enhanced.
⇒ Further research about the impact of place of birth on outcomes to school age for children born very preterm (below 32 weeks of gestation) is required.

INTRODUCTION

Excess mortality and increased neurological complications have been demonstrated in preterm infants born in non-tertiary (level 1 and level 2) hospitals without neonatal intensive care facilities in the USA,[1–3] Finland,[4] Spain,[5] Australia,[6 7] Canada[8] and England.[9 10] Possible reasons that are not mutually exclusive are that outborn infants were more unwell

prior to delivery, that perinatal care was suboptimal for those outborn or that postnatal transfer is deleterious to the infants' well-being. Previous studies have investigated the longer-term neurological consequences of outborn very preterm infants up to 2–3 years of age.[7 11–13]

Non-level-3 hospitals are often able to transfer mothers with 'stable' pathologies (where birth is not imminent) such as pre-eclampsia,[8] spontaneous rupture of membranes without labour[2 6] and small for gestation age.[2 6 8] 'Unstable' pathologies such as spontaneous labour and antepartum haemorrhage are more frequent in outborn births. This creates distortion in caseload between transferring and receiving units which introduces selection bias when trying to understand differences in outcomes according to place of birth.[2 6 8 9] In addition, the use of antenatal steroids is more prevalent in inborn births[2 7 9 10 14–17] and represents an important source of confounding between the outcomes of outborn and inborn infants; steroids being independently associated with reduced mortality and neuromorbidity.[18]

We used the EPIPAGE-2[19–21] national, population-based prospective study to examine the hypothesis that, when the influences of gestational age (GA) and antenatal steroids are controlled for, the combined outcome of survival without moderate or severe neurodevelopmental impairment at 5.5 years is not different between outborn and inborn infants.

METHODS

Study population

EPIPAGE-2 prospectively collected data on all births occurring in France in 2011 under 35 weeks GA.[19–21] Infants born in mainland France between 24 and 31 weeks of GA were eligible for inclusion in this study. Infants born at home, who had lethal congenital abnormalities or for whom antenatal steroids data were missing were excluded.

Exposure

In France, perinatal centres are categorised into level-3 units, which provide neonatal intensive care for infants requiring ongoing invasive ventilation,and non-level-3 units, which may provide some short-term invasive ventilation. National guidelines in 2011 recommended that births at less than 32 weeks of gestation or less than 1500 g occur in level-3 units,[22] building on the regionalised system of care first mandated in 1998.[23]

Outcomes

The primary outcome was survival without moderate or severe neurodevelopmental impairment at 5.5 years of age. Evaluations were performed by trained paediatricians and developmental child psychologists, and included cerebral palsy (CP), sensory (vision and hearing) and cognitive abilities. CP was classified using the Global Motor Function Classification System (GMFCS), with level 1 being mild, levels 2–3 moderate and levels 4–5 severe impairment.[24] Moderate or severe visual impairment was defined as bilateral binocular visual acuity 3.2/10, and moderate or severe hearing impairment as unilateral or bi-lateral hearing loss >40 dB not corrected or only partially corrected by hearing aids. Cognitive deficiency was measured using the full scale intelligence quotient (FSIQ) from the French version of the Wechsler Preschool and Primary Scale of Intelligence fourth Edition,[25] with moderate-to-severe impairment defined as an FSIQ 2 SD below the mean of a term-born reference group.[21] We present results for the primary outcome and survival, and for moderate-to-severe neurodevelopmental impairment among survivors.

We also investigated earlier outcomes. At discharge, we examined survival without severe neonatal morbidities (intraventricular haemorrhage grades III–IV, or cystic periventricular leukomalacia; necrotising enterocolitis, Bell stages 2–3; severe bronchopulmonary dysplasia, requiring ≥30% oxygen and/or ventilatory support at 36 weeks' GA; retinopathy of prematurity stage 3 or higher) as well as individual morbidities.[20] At age 2, we examined survival without moderate or severe sensorimotor impairment defined as CP (GMFCS levels 2–5) and/or unilateral or bilateral deafness and/or blindness, as reported by attending paediatricians. We additionally report the number of children with a parentally reported Ages and Stages Questionnaire (ASQ) score below the reference threshold in at least one of the five domains (communication abilities, gross motor skills, fine motor skills, problem solving abilities and personal-social skills).[26]

Statistical analysis

We compared potential confounding factors between outborn and inborn groups of infants, then performed conditional logistic regression to explore outcome differences using a matched cohort design to eliminate differences in GA and antenatal steroid administration between the two groups. A greedy matching algorithm without replacement was used, with exact matching on week of GA and antenatal steroid administration in the 2 weeks prior to birth (three categories: full course, defined as two doses more than 24 hours before birth, partial course, or no steroids); neither variable had missing data. As there were missing data among outcomes and covariates, all analyses were performed after multiple imputation; hence unique identifiers of matched infants were noted for subsequent use with the imputed data. The imputation model included the exposure, outcomes and matching variables, as well as variables potentially predicting non-response or the outcome. Categorical variables were imputed using logistic or multinomial regression and continuous variables using predictive mean matching. Full details are shown in online supplemental table 1. Using the entire population of infants eligible for study inclusion; we generated 50 independent imputed datasets with 30 iterations each. Data for infants previously selected by the matching process were then retained from each imputed data set for use in analyses.

Data were also weighted to account for imbalances due to varying numbers of matched inborn children; outborns were assigned a weight of one and each control subject had a weight proportional to the number of cases in its matched set divided by the number of controls in the set. Conditional logistic regression was performed with adjustment for maternal age (years), parents' socioeconomic status (using the highest level of either parent, or the mother only if she was single), nulliparous, use of infertility treatment, multiple pregnancy, tocolysis, antenatal administration of magnesium sulfate, premature rupture of membranes (PROM), spontaneous onset of labour, chorioamnionitis, pre-eclampsia, antepartum haemorrhage, caesarean section, cephalic presentation, small-for-GA and sex (all variables binary unless stated).

Analyses were performed in SAS using 'proc psmatch' for matching and 'proc MI' for imputation. Results were pooled according to Rubin's rule.[27] All statistical tests were two sided and the probability of a type 1 error (α) was set at <0.05.

Sensitivity analyses

We assessed the primary outcome in restricted populations of 24–27 weeks and 28–31 weeks of gestation to counter for potential effects from infants who were not transferred and from differences in attitude to extreme preterm birth; we also provide estimates by week of GA. Because reasons for delivery may vary between fetuses in multiple pregnancies, we repeated these analyses using the complete GA range (24–31 weeks) but restricted to singleton births only. Finally, to account for the influence of obstetric decision-making, we examined the population of 24–31 week GA fetuses alive at maternal admission to hospital. We also repeated the principal analyses using only subjects with complete data.

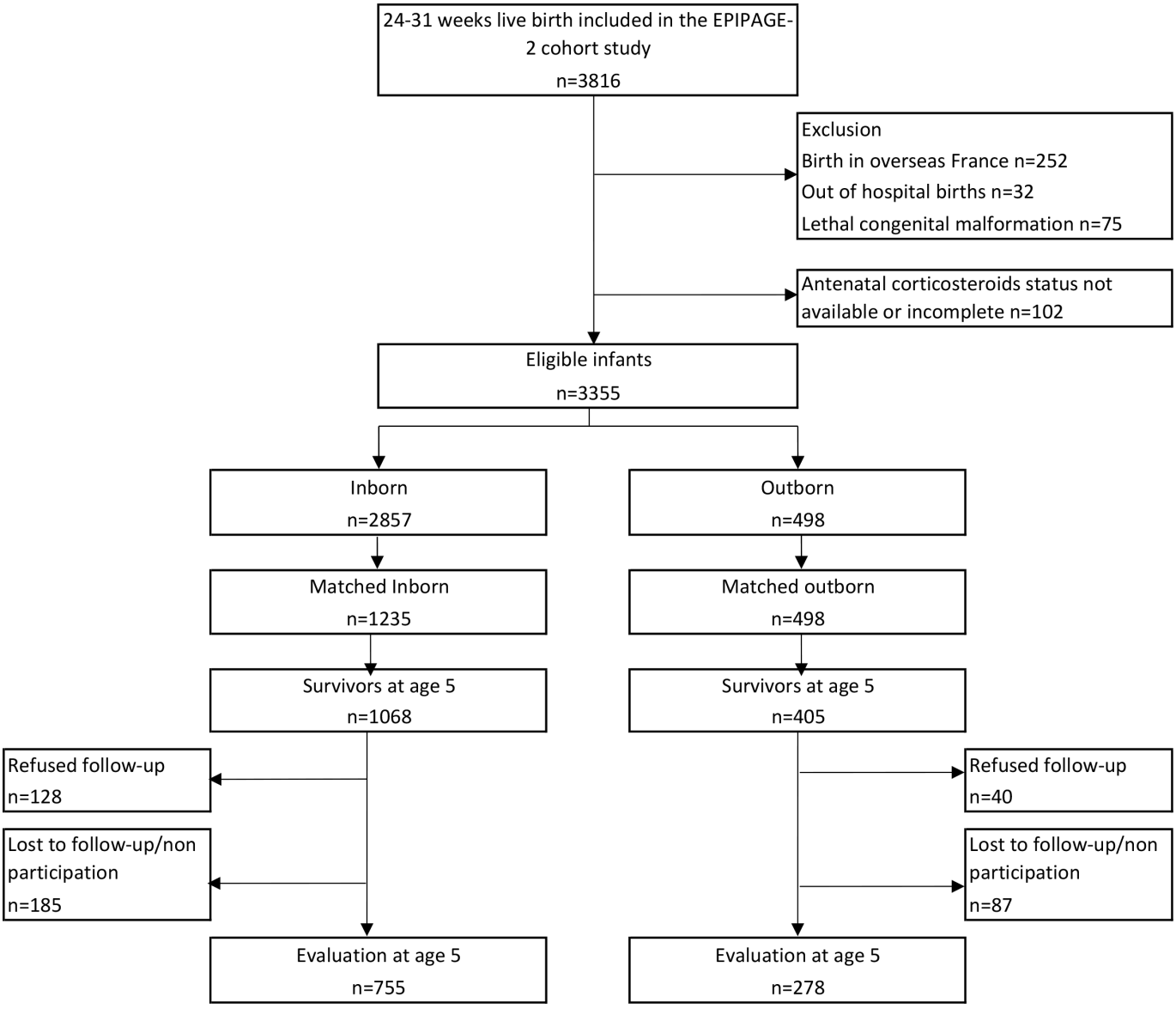

Figure 1 Flow chart of children eligible for inclusion.

Table 1 Perinatal characteristics of the initial cohort and matched outborn infants with inborn controls

	Initial cohort*				Matched cohort†				
	Inborn		Outborn		Inborn 1:n (up to 4)		Outborn		
	n=2857	%	n=498	%	n=1235	%	n=498	%	P value‡
Gestational age, week									
24	130	4.6	31	6.2	66	6.2	31	6.2	>0.999
25	233	8.2	40	8.0	91	8.0	40	8.0	
26	308	10.8	49	9.8	105	9.8	49	9.8	
27	297	10.4	41	8.2	99	8.2	41	8.2	
28	361	12.6	47	9.4	121	9.4	47	9.4	
29	401	14.0	51	10.2	108	10.2	51	10.2	
30	528	18.5	81	16.3	235	16.3	81	16.3	
31	599	21.0	158	31.7	410	31.7	158	31.7	
Maternal characteristics at birth									
Maternal age									
<25 years	507	17.8	120	24.1	224	17.9	120	24.1	0.002
25–34 years	1693	59.3	299	60.0	743	59.8	299	60.0	
>35 years	655	22.9	79	15.9	267	22.2	79	15.9	
Missing	2		0		–		–		
Mother born in France	2092	74.9	393	82.4	905	72.5	407	81.7	<0.001
Missing	63		21		–		–		
Parents' socioeconomic status§									
Professional	611	22.8	77	17.3	253	19.2	84	17.0	0.42
Intermediate	548	20.4	91	20.4	256	20.5	100	20.1	
Administrative, public service, self-employed, students	733	27.3	111	24.9	338	27.2	125	25.2	
Shop assistants, service workers	374	14.0	88	19.8	176	15.5	97	19.5	
Manual workers	338	12.6	59	13.3	159	12.8	68	13.8	
Unemployed	77	2.9	19	4.3	51	4.9	22	4.5	
Missing	176		53		–		–		
Obstetric factors									
Primiparous	1555	54.9	255	52.1	662	51.8	259	52.1	0.88
Missing	22		9		–		–		
Multiple pregnancy	973	34.1	129	25.9	399	29.4	129	25.9	0.16
Infertility treatment	524	18.5	39	8.0	199	14.5	39	8.0	<0.001
Missing	31		12		–		–		
Antenatal steroids									
No	337	11.8	244	49.0	337	49.0	244	49.0	1
Incomplete course	453	15.9	131	26.3	406	26.3	131	26.3	
Complete course	2067	72.3	123	24.7	492	24.7	123	24.7	
Tocolysis	1657	58.2	224	45.3	652	48.1	225	45.3	0.32
Missing	10		3		–		–		
Antenatal administration of magnesium sulfate	266	9.4	6	1.2	105	7.0	6	1.3	<0.001
Missing	32		9		–		–		
Premature rupture of membranes	952	33.6	88	18.3	362	27.8	93	18.7	<0.001
Missing	20		18		–		–		
Spontanous labour	1369	49.2	314	65.6	625	52.3	320	64.4	<0.001
Missing	75		19		–		–		
Chorioamnionitis	103	3.7	9	1.9	47	4.3	11	2.2	0.062
Missing	51		15		–		–		

Continued

Table 1 Continued

	Initial cohort*				Matched cohort†				
	Inborn		Outborn		Inborn 1:n (up to 4)		Outborn		
	n=2857	%	n=498	%	n=1235	%	n=498	%	P value‡
Antepartum haemorrhage	150	5.3	53	10.8	81	6.9	54	10.9	0.011
Missing	28		8		–		–		
Pre-eclampsia	513	18.4	51	10.6	234	18.2	54	10.9	<0.001
Missing	65		15		–		–		
Caesarean	1891	66.4	260	53.7	782	61.5	264	53.1	0.002
Missing	9		14		–		–		
Neonatal factors									
Cephalic presentation	1750	62.9	313	67.7	799	66.7	334	67.3	0.81
Missing	76		36		–		–		
Male sex	1503	52.6	265	53.2	651	51.4	265	53.2	0.51
Missing					–		–		
Small-for-gestational age¶	1032	36.1	124	25.0	418	32.7	124	25.0	0.002
Missing	1		2		–		–		

*Denominators vary according to the number of missing data for each variable.
†Result after multiple imputation for missing data and weighted for the variable matching ratio.
‡P values calculated using conditional logistic regression.
§Defined as the highest occupational status of the mother and father, or mother only if living alone.
¶Small-for-gestational age was defined as birth weight less than the 10th percentile for gestational age and sex based on French intrauterine 'EPOPé' growth curves (Ego 2016).

Patient and public involvement

There was no patient involvement in this study. However, EPIPAGE-2 maintains contact with the cohort through letters, newsletters and its website, and follow-up is ongoing. National parents' associations assist with the dissemination of results.

RESULTS

Of 3816 live born infants enrolled between 24 and 31 weeks of gestation in EPIPAGE-2, 3355 were eligible for inclusion in the study (figure 1); no important differences were seen with the 102 children missing information about antenatal steroid administration (online supplemental table 2). A total of 498 outborn infants were matched with 1235 of the 2857 inborn infants (2.48 inborns per outborn). A comparison of the characteristics of the matched and unmatched inborn infants is contained in online supplemental table 3.

Baseline maternal and newborn characteristics are presented in table 1. Administration of a complete course of steroids was lower for outborns (24.7%) than inborns (72.3%) in the whole population. After matching, important differences remained for maternal age, mother's country of birth, use of infertility treatment, maternal pregnancy complications and obstetric treatments, and in fetal size at birth.

Primary outcome

There was no difference in the primary outcome of survival without moderate or severe neurodevelopmental impairment at 5.5 years of age using imputed data (adjusted OR 1.09, 95% CI 0.82 to 1.44, p=0.56), as shown in table 2.

Secondary outcomes

Table 2 also shows results for the secondary outcomes. Prior to adjustment, there was a suggestion of improved survival at 5.5 years for inborns, with an unadjusted OR 1.36 (95% CI 0.99 to 1.88). This association was mitigated after accounting for potential confounders. At 2 years corrected age, survival without moderate or severe sensorimotor impairment was higher in the inborns in unadjusted analysis (OR 1.45, 95% CI 1.09 to 1.91), but this was no longer apparent after adjustment (adjusted OR 1.27, 95% CI 0.93 to 1.72). Among survivors at 2 years, there were no differences in CP (adjusted OR 0.66, 95% CI 0.21 to 1.34) or for the ASQ (adjusted OR 1.05, 95% CI 0.78 to 1.42). Prior to hospital discharge, there were no statistically significant differences in survival without severe neonatal morbidity or for individual pathologies except necrotising enterocolitis which was less frequent among inborns (3.6% compared with 5.8%, adjusted OR 0.56, 95% CI 0.32 to 0.98).

Sensitivity analyses

No statistically significant effects were seen in sensitivity analyses among those alive at the beginning of labour or when the population was restricted to singletons only. Among those born at 24–27 weeks' GA, there was evidence of higher survival without moderate-to-severe impairment at 5.5 years of age for inborns compared with

Table 2 Outcomes at age 5.5 years in a matched study of inborn and outborn children from the EPIPAGE-2 cohort according to gestational age at birth (analysis using data after multiple imputation)

	Matched cohort 1:n (up to 4)*							
	Inborn		Outborn		Inborn versus outborn			
	n=1235	%	n=498	%	Unadjusted OR (95% CI)†	P value	Adjusted OR (95% CI)†‡	P value
Primary outcomes								
Survival without severe or moderate disabilities at 5.5 years§	876	69.1	322	64.8	1.21 (0.94 to 1.57)	0.140	1.09 (0.82 to 1.44)	0.560
Secondary outcomes								
Survival at 5.5 years	1068	85.6	405	81.3	1.36 (0.99 to 1.88)	0.056	1.15 (0.83 to 1.58)	0.400
Among survivors	n=1068		n=405					
Severe or moderate disabilities at 5.5 years§	191	19.3	82	20.3	0.94 (0.66 to 1.35)	0.730	0.97 (0.66 to 1.42)	0.870
Cerebral palsy GMFCS-2/5	46	4.8	25	6.4	0.74 (0.41 to 1.36)	0.340	0.78 (0.42 to 1.46)	0.440
FSIQ <79 (<–2 SD¶)	157	16.0	66	16.5	0.97 (0.65 to 1.45)	0.870	0.98 (0.63 to 1.53)	0.940
Moderate-to-severe visual impairment	24	2.7	10	2.5	1.09 (0.40 to 2.96)	0.870	1.11 (0.41 to 3.02)	0.840
Moderate-to-severe hearing impairment	9	1.0	4	1.1	0.86 (0.24 to 3.13)	0.820	1.11 (0.29 to 4.28)	0.880
Survival at discharge without severe neonatal morbidity**	910	71.5	333	67.0	1.24 (0.97 to 1.58)	0.080	1.08 (0.83 to 1.40)	0.570
Among survivors	n=1072		n=407					
Severe cerebral lesion	65	7.0	26	6.6	1.07 (0.65 to 1.75)	0.800	1.22 (0.72 to 2.07)	0.470
Necrotising enterocolitis	41	3.6	23	5.8	0.60 (0.35 to 1.04)	0.069	0.56 (0.32 to 0.98)	0.043
Severe bronchopulmonary dysplasia	61	6.7	27	6.7	1.02 (0.61 to 1.69)	0.950	0.99 (0.57 to 1.70)	0.960
Severe retinopathy of prematurity	10	1.4	4	1.0	1.35 (0.40 to 4.60)	0.630	1.34 (0.30 to 5.90)	0.700
Survival without moderate or severe neuromotor or sensory disabilities at 2 years CA††	1026	81.9	377	75.8	1.45 (1.09 to 1.91)	0.010	1.27 (0.93 to 1.72)	0.130
Among survivors	n=1068		n=405					
Cerebral palsy GMFCS-2/5	30	3.2	19	4.9	0.64 (0.32 to 1.30)	0.220	0.66 (0.21 to 1.34)	0.250
Moderate-to-severe visual impairment	10	1.0	3	0.9	1.11 (0.13 to 9.14)	0.920	1.28 (0.15 to 10.85)	0.820
Moderate-to-severe hearing impairment	4	0.5	7	1.8	0.27 (0.06 to 1.22)	0.089	0.28 (0.04 to 2.05)	0.210
ASQ below threshold‡‡	409	41.0	149	40.7	1.01 (0.76 to 1.35)	0.930	1.05 (0.78 to 1.42)	0.750

*Result after multiple imputation for missing data and weighted for the variable matching ratio.
†ORs were calculated using conditional logistic regression.
‡OR adjusted for maternal age, mother born in France, parents' socioeconomic status, primiparous, infertility treatment, multiple pregnancy, tocolysis, antenatal administration of magnesium sulfate, context of preterm birth, caesarean section, cephalic presentation, small-for-gestational age and sex.
§Defined as at least one of: severe or moderate cerebral palsy (GMFCS level 2-5), visual (bilateral binocular visual acuity <3.2/10) or hearing (unilateral-bilateral hearing loss > 40dB not corrected or partially corrected with hearing aid) impairment, or FSIQ <2 SDs below the mean of the reference group born at term (Pierrat et al[21] 2021).
¶Cut-off of the distribution related to the reference group born at term (Pierrat et al[21] 2021).
**Severe bronchopulmonary dysplasia or necrotising enterocolitis stage 2–3 or severe retinopathy of prematurity stage >3 or any of the following severe cerebral abnormalities on cranial ultrasonography: intraventricular haemorrhage grade III or IV or cystic periventricular leukomalacia (Ancel et al[20] 2015).
††Cerebral palsy GMFCS levels 2–5 and/or unilateral or bilateral deafness and/or unilateral or bilateral blindness.
‡‡Below threshold of the United States ASQ-3 reference. Among children without cerebral palsy, deafness or blindness.
ASQ, Ages and Stages Questionnaire; CA, corrected age; FSIQ, Full Scale Intelligence Quotient; GMFCS, Gross Motor Function Classification System.

outborns (adjusted OR 1.71, 95% CI 1.05 to 2.81) but not for those born at 28–31 weeks' gestation (table 3). Between 26 and 31 weeks gestation, there was a trend towards increasing ORs with decreasing GA although all of the 95% CI included 1.0 except for at 26 weeks where the 95% CI in adjusted analysis was 1.01 to 8.24 (p=0.048). Below 26 weeks, there was no evidence of a difference between inborns and outborns (online supplemental table 4).

Results among cases with complete data (table 4) were broadly the same as the main analysis other than for CP, which showed a markedly lower odds at ages 2 (adjusted OR 0.22, 95% CI 0.10 to 0.47) and at age 5.5 (adjusted OR 0.41, 95% CI 0.19 to 0.87) years and for hearing

Table 3 Sensitivity analyses for survival without moderate-to-severe impairment at age 5.5 years in a matched study of inborn and outborn children from the EPIPAGE-2 cohort according to gestational age at birth (analysis using data after multiple imputation)

	Matched cohort 1:n (up to 4)*							
	Inborn		Outborn		Inborn versus outborn			
	n/N	%	n/N	%	Unadjusted OR (95% CI)†	P value	Adjusted OR (95% CI)†‡	P value
Survival without severe or moderate disabilities at 5.5 years§								
24–27 weeks	162/361	46.7	56/161	35.0	1.63 (1.06 to 2.51)	0.026	1.71 (1.05 to 2.81)	0.032
28–31 weeks	711/874	79.8	266/337	79.1	1.04 (0.70 to 1.54)	0.840	0.95 (0.62 to 1.45)	0.810
24–31 SA singleton	614/868	68.9	240/369	65.1	1.19 (0.88 to 1.60)	0.260	1.05 (0.75 to 1.46)	0.780
24–31 SA including alive at beginning of labour	877/1282	64.9	322/536	60.2	1.22 (0.96 to 1.56)	0.110	1.11 (0.85 to 1.45)	0.460

*Result after multiple imputation for missing data and weighted for the variable matching ratio. Matching were performed in each subgroup.
†ORs were calculated using conditional logistic regression.
‡Adjusted OR on maternal age, mother born in France, parents' socioeconomic status, primiparous, infertility treatment, multiple pregnancy, tocolysis, antenatal administration of magnesium sulfate, context of preterm birth, caesarean section, cephalic presentation, small-for-gestational age and sex.
§Severe or moderate cerebral palsy (Gross Motor Function Classification System level-2/5), visions (bilateral binocular visual acuity<3.2/10), hearing (unilateral-bilateral hearing loss >40 dB not corrected or partially corrected with hearing aid) and full-scale IQ<2 SD below the mean of the reference sample born at term (See Pierrat et al 2021).

impairment at 2 years of age (adjusted OR 0.17, 95% CI 0.07 to 0.44).

DISCUSSION

Principal results

When GA and antenatal steroids are accounted for, in a large national cohort with neurological follow-up to 5.5 years of age, no differences were identified in survival without moderate or severe neurological impairment for very preterm outborn infants compared with inborns, nor were any differences seen in individual components. This was also the case at 2 years of age. With the exception of necrotising enterocolitis, no differences were seen in neonatal morbidities.

Strengths and limitations

The major strength of the EPIPAGE 2 study is that it is a large national cohort with detailed, prospective, long-term follow-up to preschool age carried out by trained investigators. Other recent publications[2 6 9 10 28] have looked exclusively at mortality and neonatal neurological complications, which do not necessarily extrapolate to later functional ability. The follow-up rate—around 70% at 5.5 years—means our study compares favourably with other studies of outborns, for example, 62% of outborns and 69% of inborns at 1 year of age in Western Australia[7]; 57% of outborns and 77% of inborns were seen at 2–3 years in a cohort from New South Wales[11]; and under 50% were seen at 3 years of age in a Japanese study.[29] However, the loss to follow-up is potentially a limitation: not all children completed all of the tests, meaning that there were up to 40% missing data for some components of the outcome; this was addressed using multiple imputation, which has been shown to be robust even when the missing-at-random assumption is violated.[30]

Another strength is the inclusion of all live births, plus the sensitivity analysis accounting for the entire population of at risk fetuses alive at maternal admission to hospital. Results from studies not including these data are difficult to interpret.[2 10 12 13] For instance, one recent study which did not include pretransfer deaths used proportional hazards regression after propensity score matching and reported increased in-hospital mortality for inborns.[2] Our analyses showed no differences between the inborn and outborn groups regardless of which baseline population was used. We were, however, limited by an inability to consider factors like the Apgar score or cord gas results that reflect status at birth and which may be less than ideal in non-level 3 units due to suboptimal obstetric care. We also could not evaluate the potential impact of the presence of paediatric transport teams in non-level 3 units prior to delivery as these data were not collected. Furthermore, despite the importance of studying long-term outcomes, management of infants in the EPIPAGE-2 cohort may no longer be representative of current care standards. For instance, there is an increasing emphasis on the neonatal 'Golden Hour',[31] which may not have been uniformly implemented at the time in non-level-3 units. We unfortunately did not have the data to examine this, nor do we have more recent data with which to evaluate evolution of practices over time. However, long-term follow-up can only be based on historic practices; hence, the importance of trying to understand which factors might affect later outcomes.

Table 4 Outcomes at age 5.5 years in a matched study of inborn and outborn children from the EPIPAGE-2 cohort according to gestational age at birth (analysis using only subjects with complete data)

	Matched cohort 1:n (up to 4)*							
	Inborn		Outborn		Inborn vs outborn			
	n=1235	%	n=498	%	Unadjusted OR (95% CI)†	P value	Adjusted OR (95% CI)†‡	P value
Primary outcomes								
Survival without severe or moderate disabilities at 5.5 years§	551/820	64.5	188/327	57.5	1.34 (1.03 to 1.76)	0.030	1.16 (0.84 to 1.61)	0.380
Secondary outcomes								
Survival at 5.5 years	1068/1235	85.6	405/498	81.3	1.36 (0.99 to 1.88)	0.056	1.18 (0.82 to 1.71)	0.380
Among survivors	n=1068		n=405					
Severe or moderate disabilities at 5.5 years§	102/653	17.7	46/234	19.7	0.86 (0.62 to 1.21)	0.390	0.90 (0.59 to 1.37)	0.610
Cerebral palsy GMFCS-2/5	23/748	3.2	15/274	5.5	0.58 (0.33 to 1.00)	0.052	0.41 (0.19 to 0.87)	0.021
FSIQ<79 (<–2 SD¶)	82/650	14.5	33/230	14.3	1.01 (0.68 to 1.50)	0.960	1.00 (0.60 to 1.67)	0.990
Moderate-to-severe visual impairment	6/655	0.8	2/230	0.9	0.98 (0.20 to 4.35)	0.980	2.32 (0.20 to 26.4)	0.500
Moderate-to-severe hearing impairment	6/731	1.0	4/265	1.5	0.64 (0.20 to 2.03)	0.450	1.29 (0.30 to 5.57)	0.730
Secondary exploratory outcomes								
Survival at discharge without severe neonatal morbidity**	866/1235	68.1	314/498	63.1	1.25 (0.97 to 1.61)	0.086	1.17 (0.87 to 1.58)	0.300
Among survivors	n=1072		n=407					
Severe cerebral lesion	64/1057	7.0	26/396	6.6	1.06 (0.70 to 1.61)	0.770	1.34 (0.75 to 2.41)	0.320
Necrotising enterocolitis	40/1059	3.5	23/403	5.7	0.60 (0.35 to 1.03)	0.066	0.45 (0.24 to 0.84)	0.013
Severe bronchopulmonary dysplasia	57/1042	6.6	24/395	6.1	1.08 (0.67 to 1.76)	0.740	0.85 (0.48 to 1.50)	0.570
Severe retinopathy of prematurity	10/1064	1.4	4/404	1.0	1.37 (0.61 to 3.05)	0.440	2.02 (0.52 to 7.75)	0.310
Survival without severe or moderate neuromotor or sensory disabilities at 2 years CA††	1047/1235	83.8	385/498	77.3	1.51 (1.12 to 2.05)	0.008	1.55 (1.10 to 2.20)	0.014
Among survivors	n=1068		n=405					
Cerebral palsy GMFCS-2/5	15/890	2.0	15/320	4.7	0.41 (0.22 to 0.74)	0.003	0.22 (0.10 to 0.47)	<0.001
Moderate-to-severe visual impairment	3/838	0.3	1/292	0.3	0.74 (0.23 to 2.33)	0.600	1.43 (0.58 to 3.48)	0.440
Moderate-to-severe hearing impairment	3/874	0.4	6/309	1.9	0.22 (0.10 to 0.50)	<0.001	0.17 (0.07 to 0.44)	<0.001
ASQ below threshold‡‡	321/801	40.1	105/269	39.0	1.04 (0.80 to 1.37)	0.760	1.02 (0.74 to 1.42)	0.880

*Result after multiple imputation for missing data and weighted for the variable matching ratio.
†ORs were calculated using conditional logistic regression.
‡OR adjusted for maternal age, mother born in France, parents' socioeconomic status, primiparous, infertility treatment, multiple pregnancy, tocolysis, antenatal administration of magnesium sulfate, context of preterm birth, caesarean section, cephalic presentation, small-for-gestational age and sex.
§Defined as at least one of: severe or moderate cerebral palsy (GMFCS level 2-5), visual (bilateral binocular visual acuity <3.2/10) or hearing (unilateral-bilateral hearing loss > 40 dB not corrected or partially corrected with hearing aid) impairment, or FSIQ <2 SDs below the mean of the reference group born at term (Pierrat et al[21] 2021).
¶Cut-off of the distribution related to the reference group born at term (Pierrat et al[21] 2021).
**Severe bronchopulmonary dysplasia or necrotising enterocolitis stage 2–3 or severe retinopathy of prematurity stage >3 or any of the following severe cerebral abnormalities on cranial ultrasonography: intraventricular haemorrhage grade III or IV or cystic periventricular leukomalacia (Ancel et al[20] 2015).
††Cerebral palsy GMFCS levels 2–5 and/or unilateral or bilateral deafness and/or unilateral or bilateral blindness.
‡‡Below threshold of the United States ASQ-3 reference. Among children without cerebral palsy, deafness or blindness.
ASQ, Ages and Stages Questionnaire; CA, corrected age; FSIQ, Full Scale Intelligence Quotient; GMFCS, Gross Motor Function Classification System.

Interpretation

The decision to match for antenatal steroids was based on their association with reductions in neonatal death and intraventricular haemorrhage.[18] Previous studies of outborn preterm infants have noted similar patterns of increased neonatal deaths and neurological complications and the disproportional use of steroids in inborn versus outborn births.[3 5–10 15 17] Our two-step methodology, matching then adjustment, has the advantage of initially neutralising confounding by matching steroids

at the expense of tending to harmonise the characteristics of inborns and outborns. However, despite the matching process, the inborn group retained a similar predominance of 'stable' pathologies such as pre-eclampsia,[8] intrauterine growth retardation6,[8 10] preterm PROM[6 10] and chorioamnionitis[10] as seen in other studies. Similarly, the outborn deliveries featured more 'unstable' pathologies such as placental abruption6 and delivery was more frequent following spontaneous labour.[6]

The disadvantage of matching is the undesirable, and foreseeable, effect of potentially introducing a selection bias because of the assumption that there is no random error attributable to sampling variability, which is unlikely to be true.[32] Differences exist between the matched and unmatched inborns for several antenatal characteristics—particularly, the use of antenatal steroids which was higher for inborns who were not matched. There were also higher levels of tocolysis, small for GA and PROM in unmatched inborns, but more pre-eclampsia among those who were matched.

The second step of our method therefore was to adjust the point estimate using maternal and pregnancy characteristics to reduce the potential selection bias induced by matching. Both before and after adjustment, we found no difference in outcome between the groups. This suggests that, after accounting for other factors, differences in antenatal steroid administration between inborn and outborn births play an important role in influencing long-term outcomes, and that public health policies should promote greater administration of antenatal steroids for women presenting with threatened preterm delivery.

Our sensitivity analyses looked at excluding both the lowest and highest GA infants. The high level of mortality observed among outborn infants of the lowest GAs has previously been reported.[7] The 24-31 weeks' GA population had an estimated OR for the principal outcome not far from one. When we looked at only the 24–27 week infants, the adjusted estimate showed improved outcomes for inborns. Analyses performed by week of GA suggested a trend favouring inborn infants at lower GAs, although not at the GAs of 24 and 25 weeks for which attitudes in France in 2011 were known to be more mixed.[33 34] These results are consistent with other studies that suggest benefits of antenatal transfer are greater with decreasing GA.[1 7 35] Moreover, while over 80% of children were inborn and a regionalised system of care has existed in France since the 1990s,[23] there remain a subset of outborns that could potentially be avoided.[34]

At 2 years of age, there were no differences in outcomes between our inborn and outborn groups, similar to two smaller Australian studies that looked at infants of 23–28 weeks' GA[11] and 23–25 weeks' GA.[7] Similarly, there were no differences in neonatal outcomes other than for necrotising enterocolitis which was of borderline statistical significance (p=0.043) and may be a chance finding due to multiple testing; this warrants further investigation.

Generalisability

There is no consensus regarding which GAs to include in studies of outborns, with other studies using different GA ranges,[2 6 8–11 14 16 17 28] and some studies instead using a birth weight cut-off.[3–5 36] We included infants of 24–31 weeks due to the recommendation that births of less than 32 weeks should occur in a Level-3 unit[22] and because of the known poor outcomes of births at <24 weeks in France.[19] Many European and other high-income countries have similar guidelines and approaches to those of France in 2011.[37] Our results should, therefore, be relevant for such countries too.

Conclusions

Overall, there was no difference in longer-term survival to 5.5 years of age without moderate or severe neurological impairment between inborn and outborn very preterm children when GA and maternal antenatal steroids were accounted for. This suggests that antenatal steroids may be an important determinant of differences in outcome found between inborns and outborns in other studies. For infants born at the lowest GAs, however, an improved outcome was associated with birth in level 3 hospitals; this should motivate the implementation of improved protocols to enhance antenatal transfer of women delivering at these gestations.

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Data availability statement Data are available on reasonable request. The EPIPAGE-2 data are accessible to all research teams, public or private, French or foreign, subject to authorisation by the cohort Data Access Committee. The 2016 law for modernisation of the French Public Health System provides a legal framework for access to and reuse of already collected cohort data by complying with 'Reference Methodology MR-004'. Only non-nominative data defined as having a low risk of reidentification are freely accessible. All data access requests must be submitted to the EPIPAGE 2 Data Access Committee; this committee evaluates the research projects based on the following criteria: (1) methodological strengths and weaknesses (feasibility, choice of methods to achieve the objectives); (2) absence of overlap with other ongoing projects - in caseof overlap, discussions with the different teams are organised; (3) relevance of the requested data for the project and respect for confidentiality. The study protocol, the data access charter and the data access procedure can be found on the EPIPAGE-2 website (https://epipage2.inserm.fr/index.php/fr/cote-recherche/235-acces-aux-donnees-et-questionnaires). Questionnaires and data catalogues are available at (https://pandora-epipage2.inserm.fr/public/).

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Supplementary Table 1, Type of variables, model used to predict missing data, and percentages of values missing for each variable included in the imputation model.

Variables	Type of variable	Model used to predict missing data	Percentages of missing values among survivors at 5
inborn	Binary	No missing data	0%
Gestational age	Categorical	No missing data	0%
Maternal characteristics at birth			
Maternal age at birth	Categorical (3 categories)	Multinomial regression	0%
Primiparity	Binary	Logistic regression	1%
Maternal born in France	Binary	Logistic regression	1%
Living in a couple relationship	Binary	Logistic regression	5%
Parents' socio-economic status*	Categorical (5 categories)	Multinomial regression	5%
Maternal level of education	Categorical (5 categories)	Multinomial regression	6%
Obstetric factors			
Multiple pregnancy	Binary	No missing data	0%
Infertility treatment	Binary	Logistic regression	1%
Antenatal steroids	Binary	No missing data	0%
Tocolysis	Binary	Logistic regression	<1%
Antenatal administration of magnesium sulphate	Binary	Logistic regression	1%
Premature rupture of membranes	Binary	Logistic regression	<1%
Spontanous labour	Binary	Logistic regression	3%
Chorioamnionitis	Binary	Logistic regression	2%
Antepartum haemorrhage	Binary	Logistic regression	1%
Pre-eclampsia	Binary	Logistic regression	2%
Caesarean	Binary	Logistic regression	1%
Neonatal factors			
Cephalic presentation	Binary	Logistic regression	1%
Male sex	Binary	Logistic regression	0%
Small-for-gestational age†	Binary	Logistic regression	0%
Major congenital malformation	Binary	No missing data	0%
Surfactant	Binary	Logistic regression	1%
Severe cerebral lesions	Binary	Logistic regression	1%
Severe bronchopulmonary dysplasia	Binary	Logistic regression	3%
Attempted CPAP in the first 24 hours of life	Binary	Logistic regression	1%
Respiratory distress syndrome	Binary	Logistic regression	2%
Cumulative duration of mechanical ventilation	Continuous	Predictive mean matching	1%
Severe necrotising enterocolitis	Binary	Logistic regression	1%
Severe retinopathy of prematurity	Binary	Logistic regression	1%
Late onset sepsis	Binary	Logistic regression	1%
Treatment of patent ductus arteriosus with NSAIDs	Binary	Logistic regression	2%
Surgical treatment of patent ductus arteriosus	Binary	Logistic regression	4%
Breast milk at discharge	Categorical (3 categories)	Multinomial regression	7%
At 2 years corrected age			
Cerebral palsy	Categorical	Multinomial regression	16%

	(5 categories)		
Other abnormal neuro motor signs	Binary	Logistic regression	16%
Hearing disabilities	Categorical (3 categories)	Logistic regression	18%

Supplementary Table 1 (Continued)

Variables	Type of variable	Model used to predict missing data	Percentages of missing values among survivors at 5
Visual disabilities	Categorical (5 categories)	Logistic regression	22%
ASQ Communication score	Continuous	Predictive mean matching	17%
ASQ Gross motor score	Continuous	Predictive mean matching	19%
ASQ Fine motor score	Continuous	Predictive mean matching	20%
ASQ Problem solving score	Continuous	Predictive mean matching	21%
ASQ Personal-social score	Continuous	Predictive mean matching	20%
Small vocabulary stock	Binary	Logistic regression	22%
At 5½ years			
Cerebral Palsy	Categorical (5 categories)	Multinomial regression	29%
Hearing disabilities	Categorical (4 categories)	Multinomial regression	31%
Visual disabilities	Categorical (4 categories)	Multinomial regression	38%
WPPSI-IV FSIQ score	Continuous	Predictive mean matching	40%
MABC-2 Total score	Continuous	Predictive mean matching	40%
SDQ total score	Continuous	Predictive mean matching	39%

ASQ=Ages and Stages questionnaire (Squire, 2009); WPPSI-IV=Wechsler Preschool and Primary Scale of Intelligence-Fourth edition (Wechsler, 2014); FSIQ= Full-Scale Intelligence quotient; MABC-2=Movement Assessment Battery for Children- Second Edition (Henderson, 2007); SDQ= Strengths and difficulties questionnaire (Goodman, 1997).

All variables were included as a predictor of all imputation models.

* Defined as the highest occupational status between occupations of the mother and the father, or mother only if living alone.

† Small-for- gestational age was defined as birth weight less than the 10th percentile for gestational age and sex based on French intrauterine growth curves (Ego, 2016).

Supplementary Table 2, Comparison of eligible infants and those missing information about antenatal corticosteroid administration.

	Eligible infants		**Antenatal steroids not available or incomplete data**		Chi2
	n=3355		n=102		p-value
Gestational age, week					
24	161/3355	4.8	6/102	5.9	0.36
25	273/3355	8.1	9/102	8.8	
26	357/3355	10.6	13/102	12.7	
27	338/3355	10.1	16/102	15.7	
28	408/3355	12.2	8/102	7.8	
29	452/3355	13.5	8/102	7.8	
30	609/3355	18.2	19/102	18.6	
31	757/3355	22.6	23/102	22.5	
Maternal characteristics at birth					
Maternal age					
<25 years	627/3353	18.7	17/102	16.7	0.87
25-34 years	1992/3353	59.4	62/102	60.8	
≥35 years	734/3353	21.9	23/102	22.5	
Mother born in France	2485/3271	76.0	76/95	80.0	0.87
Parents' socio-economic status*					
Professional	688/3126	22.0	16/83	19.3	0.86
Intermediate	639/3126	20.4	19/83	22.9	
Administrative, public service, self-employed, students	844/3126	27.0	22/83	26.5	
Shop assistants, service workers	462/3126	14.8	10/83	12.0	
Manual workers	397/3126	12.7	12/83	14.5	
Unemployed	96/3126	3.1	4/83	4.8	
Obstetric factors					
Primiparous	1810/3324	54.5	47/97	48.5	0.50
Infertility treatment	563/3312	17.0	17/93	18.3	0.75
Antenatal steroids					
No	581/3355	17.3		-	
Incomplete course	584/3355	17.4		-	
Complete course	2190/3355	65.3		-	
Tocolysis	1881/3342	56.3	41/92	44.6	0.026
Antenatal administration of magnesium sulphate	272/3314	8.2	5/93	5.4	0.32
Premature rupture of membranes	1040/3317	31.4	26/96	27.1	0.37
Spontanous labour	1683/3261	51.6	44/89	49.4	0.69
Chorioamnionitis	112/3289	3.4	6/90	6.7	0.10
Antepartum haemorrhage	203/3319	6.1	5/89	5.6	0.85
Pre-eclampsia	564/3275	17.2	17/92	18.5	0.75
Caesarean section	2151/3332	64.6	63/101	62.4	0.65
Multiple pregnancy	1102/3355	32.8	35/102	34.3	0.76
Neonatal factors					
Cephalic presentation	2063/3243	63.6	65/94	69.1	0.27
Male sex	1768/3355	52.7	62/102	60.8	0.11
Small-for-gestational age†	1156/3352	34.5	34/102	33.3	0.81

* Defined as the highest occupational status of the mother and father, or mother only if living alone.

† Small-for- gestational age was defined as birth weight less than the 10th percentile for gestational age and sex based on French intrauterine "EPOPé" growth curves (Ego 2016).

Supplementary Table 3, Comparison between matched and unmatched inborn infants**.**

	Matched Inborn n=1235		**Unmatched Inborn** n=1622		p-value
Gestational age, week					
24	66/1235	5.3	64/1622	3.9	<.0001
25	91/1235	7.4	142/1622	8.8	
26	105/1235	8.5	203/1622	12.5	
27	99/1235	8.0	198/1622	12.2	
28	121/1235	9.8	240/1622	14.8	
29	108/1235	8.7	293/1622	18.1	
30	235/1235	19.0	293/1622	18.1	
31	410/1235	33.2	189/1622	11.7	
Maternal characteristics at birth					
Maternal age					
<25 years	224/1234	18.2	283/1621	17.5	0.35
25-34 years	743/1234	60.2	950/1621	58.6	
≥35 years	267/1234	21.6	388/1621	23.9	
Mother born in France	888/1205	73.7	1204/1589	75.8	0.30
Parents' socio-economic status*					
Professional	241/1148	21.0	370/1533	24.1	0.075
Intermediate	243/1148	21.2	305/1533	19.9	
Administrative, public service, self-employed, students	315/1148	27.4	418/1533	27.3	
Shop assistants, service workers	163/1148	14.2	211/1533	13.8	
Manual workers	142/1148	12.4	196/1533	12.8	
Unemployed	44/1148	3.8	33/1533	2.2	
Obstetric factors					
Primiparous	658/1223	53.8	897/1612	55.6	0.32
Multiple pregnancy	399/1235	32.3	574/1622	35.4	0.085
Infertility treatment	198/1221	16.2	326/1605	20.3	0.006
Antenatal steroids					
No	337/1235	27.3	0/1622	0.0	0.006
Incomplete course	406/1235	32.9	47/1622	2.9	
Complete course	492/1235	39.8	1575/1622	97.1	
Tocolysis	651/1231	52.9	1006/1616	62.3	<0.001
Antenatal administration of magnesium sulphate	104/1216	8.6	162/1609	10.1	0.17
Premature rupture of membranes	359/1222	29.4	593/1615	36.7	<0.001
Spontanous labour	614/1195	51.4	755/1587	47.6	0.047
Chorioamnionitis	44/1207	3.6	59/1599	3.7	0.95
Antepartum haemorrhage	80/1223	6.5	70/1606	4.4	0.01
Pre-eclampsia	229/1207	19.0	284/1585	17.9	0.48
Caesarean	781/1229	63.5	1110/1619	68.6	0.005
Neonatal factors					
Cephalic presentation	779/1202	64.8	971/1579	61.5	0.073
Male sex	651/1235	52.7	852/1622	52.5	0.92
Small-for-gestational age‡	418/1235	33.8	614/1621	37.9	0.026

* Defined as the highest occupational status of the mother and father, or mother only if living alone.

‡ Small-for- gestational age was defined as birth weight less than the 10th percentile for gestational age and sex based on French intrauterine "EPOPé" growth curves (Ego 2016).

Supplementary Table 4: Survival without moderate-severe impairment at age 5½ years in a matched cohort of children from EPIPAGE-2 according to gestational age at birth.

	Matched cohort 1:n (up to 4)[a]				Inborn vs outborn			
	Inborn		Outborn					
	n/N	%	n/N	%	Unadjusted OR (95% CI)[b]	p-value	Adjusted OR (95% CI)[b,c]	p-value
Survival without severe or moderate disabilities at 5.5 years[c]								
24 weeks	9/66	14.0	3/31	11.5	1.27 (0.29-5.46)	0.75	*Did not converge*	
25 weeks	36/91	38.3	13/40	34.0	1.21 (0.49-2.95)	0.68	0.91 (0.27-3.08)	0.89
26 weeks	58/105	59.0	19/49	39.0	2.25 (1.01-5.06)	0.05	2.88 (1.01-8.24)	0.048
27 weeks	61/99	65.1	20/41	48.8	1.96 (0.87-4.44)	0.11	2.50 (0.77-8.12)	0.13
28 weeks	90/121	72.9	32/47	68.9	1.22 (0.53-2.80)	0.65	1.42 (0.45-4.52)	0.55
29 weeks	86/108	77.0	37/51	73.0	1.23 (0.48-3.18)	0.67	1.29 (0.34-4.92)	0.71
30 weeks	185/235	77.5	66/81	81.7	0.77 (0.37-1.61)	0.49	0.78 (0.34-1.80)	0.55
31 weeks	348/410	83.8	130/158	82.8	1.07 (0.57-2.03)	0.82	1.03 (0.51-2.12)	0.93

[a] Result after multiple imputation for missing data and weighted for the variable matching ratio. Matching were performed in each subgroup.

[b] OR were calculated using conditional logistic regression.

[c] OR adjusted for maternal age, mother born in France, parents' socio-economic status, primiparous, infertility treatment, multiple pregnancy, tocolysis, antenatal administration of magnesium sulphate, context of preterm birth, caesarean section, cephalic presentation, small-for-gestational age and sex.

[d] Severe or moderate cerebral palsy (Gross Motor Function Classification System level-2/5), visions (bilateral binocular visual acuity<3.2/10), hearing (uni-bilateral hearing loss > 40dB not corrected or partially corrected with hearing aid), and full-scale intelligence quotient < 2 standard deviations below the mean of the reference sample born at term (See Pierrat 5 ans).