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EPICE cohort: two-year neurodevelopmental outcomes after very preterm birth

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/archdischild-2019-317418).

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Received 15 April 2019
Revised 8 October 2019
Accepted 22 October 2019
Published Online First 5 November 2019

ABSTRACT

Objective To determine whether the variation in neurodevelopmental disability rates between populations persists after adjustment for demographic, maternal and infant characteristics for an international very preterm (VPT) birth cohort using a standardised approach to neurodevelopmental assessment at 2 years of age.

Design Prospective standardised cohort study.

Setting 15 regions in 10 European countries.

Patients VPT births: 22^{+0}–31^{+6} weeks of gestation.

Data collection Standardised data collection tools relating to pregnancy, birth and neonatal care and developmental outcomes at 2 years corrected age using a validated parent completed questionnaire.

Main outcome measures Crude and standardised prevalence ratios calculated to compare rates of moderate to severe neurodevelopmental impairment between regions grouped by country using fixed effects models.

Results Parent reported rates of moderate or severe neurodevelopmental impairment for the cohort were: 17.3% (ranging 10.2%–26.1% between regions grouped by country) with crude standardised prevalence ratios ranging from 0.60 to 1.53. Adjustment for population, maternal and infant factors resulted in a small reduction in the overall variation (ranging from 0.65 to 1.30).

Conclusion There is wide variation in the rates of moderate to severe neurodevelopmental impairment for VPT cohorts across Europe, much of which persists following adjustment for known population, maternal and infant factors. Further work is needed to investigate whether other factors including quality of care and evidence-based practice have an effect on neurodevelopmental outcomes for these children.

What is already known on this topic?

- Rates and degrees of neurodevelopmental impairment for babies born very preterm vary widely between studies and across populations.
- International comparisons are complicated by a lack of standardised data collection, differences in assessment methods, definitions, registration and reporting.

What this study adds?

- Using a standardised method, wide variation in the rates of neurodevelopmental impairment at 2 years corrected age were found across European countries.
- Adjustment for pregnancy, maternal sociodemographic and health, perinatal and neonatal morbidity factors had little impact on this variation.

INTRODUCTION

Significant advances in neonatal care since the 1980s resulted in increased survival rates for babies born very preterm (VPT: $<32^{+0}$ weeks' gestation), predominantly for those born extremely preterm (EPT: $<28^{+0}$ weeks' gestation).[1] Survival rates for EPT babies born in the 21st century have continued to rise resulting in greater numbers of VPT survivors.[2 3] There remains growing concern about the risk for residual disability in this population with rates of up to one-third of VPT survivors having neurodevelopmental impairment (NDI) at 2 years.[4 5]

Rates of impairment for children born VPT vary widely across studies.[1 6 7] It is unclear how much of this variation is due to differences in perinatal care, healthcare systems, populations or methodologies between studies. International comparisons to date are based on grouped data using meta-analyses that have not taken into account differences in population denominators.[8] In addition, different methods and measures have been used to classify developmental outcomes, thus making it difficult to estimate an international rate of impairment or identify real between-country differences.[9 10] The Effective Perinatal Intensive Care in Europe (EPICE) collaboration investigates outcomes following VPT birth in 11 European countries using a standardised approach to data collection. This allows, for the first time, a pan-European standardised comparison of VPT outcomes. Here we present neurodevelopmental outcomes at 2 years corrected age for this cohort and explore rates of NDI between countries.

METHODS

Study design

The EPICE cohort is a geographically defined prospective study of all VPT stillbirths and live births from 22^{+0} to 31^{+6} weeks of gestation born

Linked

► http://dx.doi.org/10.1136/fetalneonatal-2019-318444

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To cite: Draper ES, Zeitlin J, Manktelow BN, *et al*. *Arch Dis Child Fetal Neonatal Ed* 2020;**105**:F350–F356.

in 19 regions in 11 European countries covering 850 000 births annually.[11] Regions were selected with respect to geographic and organisational diversity, feasibility and sample size considerations. Data from obstetric and neonatal records were collected on births over the period April 2011 and September 2012. At 2 years corrected age, the parents of surviving children who had consented to follow up were sent a questionnaire to assess their child's health and neurodevelopmental outcomes.

Ethics

Parental consent was obtained for participation in the study. Authorisations for the European database: French Advisory Committee on Use of Health Data in Medical Research (N° 13.020 on 24 January 2013) and the French National Commission for Data Protection and Liberties (N° DR-2013–194 on 10 April 2013).

Study population

Our study population includes children whose families responded to a follow-up questionnaire at 2 years corrected age in 15 of 19 EPICE regions across 10 countries. Four regions were excluded: three French regions who used a different outcome assessment and UK Northern Region, which achieved a low response rate (<30%) resulting in a small and potentially biassed sample. Infants with severe congenital anomalies were also excluded due to regional variations in screening policies.[11]

Perinatal data collection

Investigators abstracted data from obstetric and neonatal records using a pretested standardised questionnaire. Gestational age was defined as the best obstetric assessment based on information for last menstrual period and antenatal ultrasounds. Inclusions were cross-checked against delivery ward registers or other external data sources. Data were collected up until discharge home from hospital or into long-term care or death.[11]

Parental questionnaire at 2 years corrected age

The parent questionnaire collected data on each child's health and healthcare use, neurodevelopmental outcomes and growth, as well as sociodemographic information. This questionnaire was either postal with a freepost return envelope enclosed or handed to parents for completion at their child's routine 2-year follow-up appointment. Questionnaires were translated as required, back translated and pretested in relevant regions. Reminders were sent via mail and/or phone in accordance with ethics approvals. To maximise response rates in some regions, non-responding parents were offered a telephone interview.[12]

Two-year assessment: measures

Parents were asked five forced-choice items from which impairment in gross motor function, hearing and vision were classified using standard criteria.[13 14] This scale has been used in clinical practice across the UK since the late 1990s. Severe hearing impairment was classified if the child was deaf or had functional hearing loss requiring correction with aids but still had difficulty hearing and severe visual impairment if the child was blind or able to see light only. Children unable to: walk without assistance or aids or sit or hold their head up without support were classified with severe gross motor impairment. A composite outcome of severe neurosensory impairment (NSI) was derived for children with one or more of severe hearing, vision or gross motor impairment.

Non-verbal cognitive (NVC) development was assessed using the non-verbal cognition scale of the Parent Report of Children's Abilities-Revised (PARCA-R),[15 16] a well-validated parent questionnaire of cognitive and language development at 2 years of age that has good diagnostic utility for identifying VPT infants with developmental delay (scores <-2 SD) on Gold Standard tests.[17] The NVC scale comprises 34 forced choice items scored 0/1 from which a total NVC score is derived. Where there were ≤4 missing items, these were substituted with the average NVC score across completed items.[18] NVC scores were not calculated for those with more than four missing items. Validated cut-off scores were based on UK data from a term-born cohort where children with NVC scores <22, corresponding with scores <2.5th percentile, were classified as having moderate to severe NVC impairment.[18] The full PARCA-R was not used because the validated language component was not available in all countries.

The composite primary outcome of moderate to severe NDI was derived for children with severe NSI and/or moderate to severe NVC impairment.

Analysis strategy

Survival rates and response rates at 2 years were compared across regions, grouped by country and maternal and infant characteristics of responders versus non-responders were reviewed. Neurodevelopmental outcomes were computed by country for the total sample and for subgroups of children born VPT and EPT to facilitate comparisons with other published studies. As the PARCA-R has been validated for use in VPT children aged 22–26 months,[15 16 18] a sensitivity analysis was carried out to investigate the impact of the timing of parental assessment.

To compare outcomes between countries, the ratio of observed to expected number of children with each outcome (standardised prevalence ratio (SPR)) was used to take into consideration differences in maternal, pregnancy and infant characteristics. The expected number of children with any outcome was calculated using effect parameterisation[19]: that is, the average prevalence observed across all countries based on the mean value of the log odds across all countries. Ninety-five per cent CIs were calculated using the percentile bootstrap method by resampling observations within each country with replacement. Variables selected for the adjusted models were based on clinical knowledge and the scientific literature on characteristics likely to affect longer term outcomes[2 5 8 20 21] and previous findings from our cohort.[11 22] Fixed effects models were selected for the adjusted models as previous work has indicated the heterogeneity between countries.[23]

RESULTS

Of the cohort of 6064 live-born VPT infants, 5214 (85.9%) were alive at 2 years corrected age as shown in table 1 (regions grouped by country), and questionnaires were returned for 3294 (63.2%), ranging from 47.2% in Belgium to 99.3% in Estonia. Factors associated with non-response were younger maternal age, foreign-born mother, multiparous mother, singleton pregnancy and prelabour preterm rupture of the membranes (table 2). There were no significant differences in gestational age or neonatal outcomes between responders and non-responders. Significance tests were adjusted by country because of potential heterogeneity. There was no evidence of a relationship between the number of morbidities observed for a child and the probability of loss to follow-up: p=0.54 from a logistic regression model. Further investigation also provided no evidence for this to vary by country: p=0.69. A more detailed

Table 1 VPT infants included in the EPICE cohort and follow-up rates at 2 years corrected age

	Total VPT live births	VPT infants discharged alive from neonatal care		Deaths following discharge and prior to 2 years corrected age		Responses at 2 years corrected age*	
Country (region)	N	n	%	n	%	n	%
Belgium (Flanders)	749	651	86.9	0	0.0	307	47.2
Denmark (Eastern region)	348	286	82.2	0	0.0	180	62.9
Estonia (whole country)	151	140	92.7	2	1.4	137	99.3
Germany (Hesse, Saarland)	735	645	87.8	5	0.8	421	65.8
Italy (Emilia, Lazio, Marche)	1111	961	86.5	6	0.6	722	75.6
The Netherlands (East-Central)	392	329	83.9	0	0.0	229	69.6
Poland (Wielkopolska)	299	236	78.9	1	0.4	189	80.4
Portugal (Lisbon, Northern)	719	606	84.3	2	0.3	408	67.5
UK (East Midlands, Yorkshire)	1297	1145	88.3	5	0.4	540	47.4
Sweden (Stockholm region)	263	237	90.1	1	0.4	161	68.2
Total	**6064**	**5236**	**86.3**	**22**	**0.4**	**3294**	**63.2**

*Response rates calculated as a per cent of eligible infants (discharged alive and surviving to 2 years corrected age).
EPICE, Effective Perinatal Intensive Care in Europe; VPT, very preterm.

description of the responders' characteristics by country can be found in online supplementary table S1.

Table 3 shows the prevalence of moderate to severe impairment overall and by country. Overall impairment prevalence rates were as follows: 17.3% for the primary outcome of moderate or severe NDI, 5.4% for severe NSI and 15.3% for moderate to severe NVC impairment. There were wide variations in prevalence with rates of moderate to severe NDI ranging

Table 2 Characteristics associated with loss to follow-up at 2 years corrected age: EPICE cohort

	Non-responders		Responders			
Characteristics	N	%	N	%	P value	P value*
Mother, pregnancy, delivery	1633		2739			
Maternal age (years)						
≤24	419	25.8	323	11.8	<0.001	<0.001
25–34	842	51.8	1573	57.6		
≥35	364	22.4	835	30.6		
Parity first child	812	50.0	1651	60.6	<0.001	<0.001
Multiple pregnancy	275	16.9	533	19.5	0.03	0.02
PPROM	433	27.4	665	24.7	0.05	0.03
Pre-eclampsia/eclampsia/HELLP	273	17.3	472	17.4	0.92	0.71
Received antenatal steroids	1440	89.1	2474	91.0	0.03	0.14
Born in the country†	649	66.8	1815	84.5	<0.001	<0.001
Infant, postneonatal care, morbidity	1920		3294			
Gestational age at birth (weeks)						
23–25	166	8.7	263	8.0	0.02	0.14
26–27	275	14.3	580	17.6		
28–29	517	26.9	859	26.1		
30–31	961	50.1	1592	48.3		
Birth weight – less than 750 g	151	7.9	285	8.7	0.32	0.40
Male	1038	54.1	1754	53.3	0.56	0.94
SGA						
<3rd percentile	380	19.8	665	20.2	0.83	0.96
3–<10th percentile	223	11.6	396	12.0		
≥10th percentile	1316	68.6	2233	67.8		
IVH (grade III or IV) – PVL	132	7.0	207	6.4	0.38	0.32
Severe NEC (requiring surgery or peritoneal drainage)	39	2.0	63	1.9	0.77	0.59
ROP (grade III, IV or V)	65	3.4	154	4.7	0.03	0.13
Bronchopulmonary dysplasia‡	254	13.5	433	13.3	0.86	0.06
Any severe morbidity	212	11.3	366	11.3	0.99	0.79

PPROM: prolonged preterm rupture of membranes; HELLP, HELLP syndrome; SGA, small for gestational age; IVH, intraventricular haemorrhage; PVL, periventricular leukomalacia; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity.
*Adjusted on region of birth.
†Without UK.
‡BPD – oxygen or respiratory support at 36 weeks' GA.
EPICE, Effective Perinatal Intensive Care in Europe; GA, gestational age.

Table 3 Prevalence of moderate and severe impairments and developmental delays at 2 years corrected age for the EPICE cohort

		Neurodevelopmental impairment	Neurosensory impairment*	Cognitive impairment
Country (region(s))	Number of responses	n/N (%)	n/N (%)	n/N (%)
Belgium (Flanders)	307	58/300 (19.3)	14/302 (4.6)	57/302 (18.9)
Denmark (Eastern region)	180	31/176 (17.6)	4/177 (2.3)	27/179 (15.1)
Estonia (whole country)	137	17/133 (12.8)	8/133 (6)	14/137 (10.2)
Germany (Hesse, Saarland)	421	57/409 (13.9)	27/414 (6.5)	49/415 (11.8)
Italy (Emilia, Lazio, Marche)	722	116/713 (16.3)	39/711 (5.5)	104/721 (14.4)
The Netherlands (East-Central)	229	23/226 (10.2)	7/228 (3.1)	21/227 (9.3)
Poland (Wielkopolska)	189	49/188 (26.1)	17/187 (9.1)	46/187 (24.6)
Portugal (Lisbon, Northern)	408	65/389 (16.7)	12/392 (3.1)	60/404 (14.9)
UK (East Midlands, Yorkshire)	540	96/455 (21.1)	41/509 (8.1)	81/468 (17.3)
Sweden (Stockholm region)	161	32/157 (20.4)	4/159 (2.5)	32/159 (20.1)
Total	3294	544/3146 (17.3)	173/3212 (5.4)	491/3199 (15.3)

*If the response to one of either motor, hearing or visual impairment was missing and the other two domains were not reported as severe impairment, then the response was included in the denominator. If severe impairment was reported for any of the domains, then the response was included in both the numerator and denominator.
EPICE, Effective Perinatal Intensive Care in Europe.

from 10.2% in the Netherlands region to 26.1% in the Polish region, severe NSI ranging from 2.3% in the Danish region to 9.1% in the Polish region and moderate to severe NVC impairment ranging from 9.3% in the Netherlands to 24.6% in Poland. Rates of impairment for babies born $<27^{+0}$ weeks and 27^{+0}–31^{+6} weeks were (respectively): 26.4% and 15.6% for moderate or severe NDI, 10.8% and 4.4% for severe NSI and 23.3% and 13.9% for moderate to severe NVC impairment. For babies born $<28^{+0}$ weeks and 28^{+0}–31^{+6} weeks were (respectively): 24.8% and 14.7% for moderate or severe NDI, 10.1% and 3.8% for severe NSI and 22.1% and 13.0% for moderate to severe NVC impairment. Individual country details are provided in online supplementary tables S2a and S2b.

A sensitivity analysis to investigate the impact of late parental assessment on outcomes showed there were no significant differences for any outcome at country level, although the rate of moderate to severe NVC impairment in the total cohort was significantly lower for parents who completed questionnaires after 26 months compared with 22–26 months (8.5% vs 15.9%) resulting in a significantly lower rate of moderate to severe NDI (11.4% vs 17.7%) (online supplementary table S3).

SPRs with 95% CIs for the three outcomes are presented in table 4. The crude SPR for moderate or severe NDI ranged from a significantly lower rate of 0.60 (95% CI 0.39 to 0.83) in the Netherlands region to a significantly higher rate of 1.53 (95% CI 1.19 to 1.92) in the Polish region. Adjustment for maternal sociodemographic and health characteristics had little effect on this overall variation, but addition of infant factors resulted in a reduction of the SPR for the Polish region to 1.17 (95% CI 0.90 to 1.47) and a small increase in the SPR for the Netherland's region to 0.65 (95% CI 0.42 to 0.93) with the overall variation ranging from this to 1.30 (95% CI 0.87 to 1.76) in the Danish region. Adjustment for infant factors had the largest effect on the SPRs for severe NSI particularly in the Polish cohort, where these factors accounted for the excess in the crude rates of severe NSI: reducing from 1.98 (95% CI 1.18 to 4.63) to 1.08 (95% CI 0.63 to 3.05). Adjustment for maternal, pregnancy and infant factors had little effect on the variation between countries for moderate or severe NVC impairment except for the Polish region where the SPR reduced from 1.63 (95% CI 1.26 to 2.05) in the crude model to 1.29 (95% CI 0.99 to 1.66) in the final model.

DISCUSSION

The EPICE study provides novel standardised comparisons of neurodevelopmental outcome at 2 years corrected age[15 16 24] in a large population-based European cohort of VPT children. While recognising that there are a wide range of outcomes that are important for the future health and well-being of VPT children, this study has focused on severe NDI as a predictor of adverse long-term outcome for VPT populations. Despite using a standardised methodology, we found wide variation in moderate or severe NDI across countries (grouped by region), with a rate 2.5 times higher in the region from Poland compared with the region in the Netherlands in line with the levels of severe morbidity at discharge from neonatal care in this cohort.[22]

Following adjustment for maternal demographic, pregnancy and infant factors, the variation in the SPR for moderate to severe NDI was reduced by around a quarter. However, while there was little or no effect of this adjustment on most country's SPR for moderate to severe NDI, the SPR for the Polish region was reduced by around a quarter, whereas for the Danish regions, the SPR was increased by a quarter. Examination of the variation in outcomes showed that the reduction in the variation in the SPR for moderate and severe NDI was for NVC impairment alone which is unsurprising given the low frequency of severe NSI relative to cognitive impairment and their likely perinatal origins. The remaining variation in SPRs suggests that there may be residual differences in the quality of care provision, treatment and provision of follow-up services for VPT infants across Europe that requires further investigation.

Direct comparison of our findings with the same gestation specific cohort in EPIPAGE2[25] showed slightly higher levels of moderate or severe NSI in the EPICE study 3.7% compared with 5.4%, respectively. However, few studies have focused on our broad gestational age group and methodological variations[10] making direct comparison of our findings with other cohorts challenging. Although only 15.5% of our cohort was <28 weeks, this group constituted 26% of the children with impairments. Nonetheless, almost three-quarters of the children with impairments were born between 27 and 31 weeks, underscoring the importance of including this broader group in research to mitigate NDI. In a recent meta-analysis[6] of neurodevelopmental outcomes in VPT or very low birth weight (<1500 g) cohorts, rates of moderate to severe NVC impairment were 8.2% overall: almost half the rate found in our study (15.3% ranging from 9.3% to 24.6% by

Table 4 Crude and adjusted standardised prevalence ratios for neurodevelopmental outcomes at 2 years corrected age by country: compared with overall EPICE cohort

Country (region(s))	SPR* (95% CI)		SPR† (95% CI)		SPR‡ (95% CI)	
Neurodevelopmental impairment						
Belgium (Flanders)	1.14	(0.90 to 1.41)	1.14	(0.90 to 1.44)	1.23	(0.95 to 1.58)
Denmark (Eastern region)	1.04	(0.72 to 1.39)	1.14	(0.79 to 1.55)	1.30	(0.87 to 1.76)
Estonia (whole country)	0.75	(0.43 to 1.10)	0.70	(0.40 to 1.06)	0.71	(0.43 to 1.06)
Germany (Hesse, Saarland)	0.82	(0.63 to 1.04)	0.84	(0.65 to 1.07)	0.82	(0.62 to 1.05)
Italy (Emilia, Lazio, Marche)	0.96	(0.80 to 1.17)	0.96	(0.80 to 1.20)	1.06	(0.87 to 1.31)
The Netherlands (East-Central)	0.60	(0.39 to 0.83)	0.67	(0.44 to 0.94)	0.65	(0.42 to 0.93)
Poland (Wielkopolska)	1.53	(1.19 to 1.92)	1.36	(1.06 to 1.74)	1.17	(0.90 to 1.47)
Portugal (Lisbon, Northern)	0.98	(0.79 to 1.22)	0.94	(0.74 to 1.16)	0.99	(0.78 to 1.24)
UK (East Midlands,orkshire)	1.24	(1.03 to 1.49)	1.27	(1.05 to 1.57)	1.15	(0.95 to 1.41)
Sweden (Stockholm region)	1.20	(0.88 to 1.57)	1.16	(0.81 to 1.55)	1.11	(0.79 to 1.50)
Neurosensory impairment						
Belgium (Flanders)	1.01	(0.56 to 2.33)	0.93	(0.50 to 3.44)	1.17	(0.66 to 3.74)
Denmark (Eastern region)	0.49	(0.13 to 1.05)	0.57	(0.15 to 1.84)	0.68	(0.00 to 2.11)
Estonia (whole country)	1.31	(0.64 to 3.06)	1.37	(0.68 to 4.75)	1.39	(0.76 to 4.11)
Germany (Hesse, Saarland)	1.42	(1.00 to 3.89)	1.57	(1.07 to 5.48)	1.89	(1.25 to 6.54)
Italy (Emilia, Lazio, Marche)	1.20	(0.85 to 3.26)	1.19	(0.83 to 4.00)	1.29	(0.88 to 3.75)
The Netherlands (East-Central)	0.67	(0.23 to 1.50)	0.73	(0.24 to 2.34)	0.63	(0.22 to 2.08)
Poland (Wielkopolska)	1.98	(1.18 to 4.63)	1.74	(0.97 to 5.62)	1.08	(0.63 to 3.05)
Portugal (Lisbon, Northern)	0.67	(0.38 to 1.87)	0.67	(0.38 to 2.38)	0.77	(0.43 to 2.54)
UK (East Midlands, Yorkshire)	1.75	(1.29 to 5.18)	1.79	(1.27 to 6.32)	1.55	(1.13 to 4.38)
Sweden (Stockholm region)	0.55	(0.14 to 1.27)	0.45	(0.00 to 1.11)	0.42	(0.00 to 1.06)
Cognitive impairment						
Belgium (Flanders)	1.25	(0.99 to 1.56)	1.27	(1.00 to 1.61)	1.34	(1.03 to 1.73)
Denmark (Eastern region)	1.00	(0.68 to 1.37)	1.11	(0.73 to 1.52)	1.26	(0.82 to 1.73)
Estonia (whole country)	0.68	(0.35 to 0.99)	0.63	(0.33 to 0.95)	0.63	(0.33 to 0.94)
Germany (Hesse, Saarland)	0.78	(0.58 to 1.00)	0.80	(0.59 to 1.03)	0.76	(0.55 to 0.98)
Italy (Emilia, Lazio, Marche)	0.95	(0.80 to 1.15)	0.94	(0.77 to 1.15)	1.04	(0.84 to 1.29)
The Netherlands (East-Central)	0.61	(0.40 to 0.87)	0.70	(0.46 to 1.01)	0.63	(0.43 to 1.00)
Poland (Wielkopolska)	1.63	(1.26 to 2.05)	1.44	(1.11 to 1.84)	1.29	(0.99 to 1.66)
Portugal (Lisbon, Northern)	0.98	(0.78 to 1.23)	0.92	(0.73 to 1.15)	0.94	(0.75 to 1.17)
UK (East Midlands, Yorkshire)	1.14	(0.92 to 1.41)	1.17	(0.91 to 1.46)	1.08	(0.84 to 1.35)
Sweden (Stockholm region)	1.33	(0.98 to 1.74)	1.28	(0.91 to 1.71)	1.23	(0.88 to 1.66)

*Empty model.
†Mother's age, native, parity, multiple, prom, eclampsia, antenatal steroids and mother's education.
‡As[1] plus week's gestational age, small for gestational age, sex, apgar and any neonatal morbidity (as listed in table 2) plus severe congenital anomaly.
EPICE, Effective Perinatal Intensive Care in Europe; SPR, standardised prevalence ratio.

country). However, this meta-analysis included VPT infants and more mature babies born with very low birth weight (VLBW). To allow for a more direct comparison with other studies, we investigated impairment rates for the cohort split at 27 and 28 weeks' gestation. A similar rate of NDI was found in the national Swedish EXPRESS cohort of babies born <27 weeks' gestation[20] (27% compared with 26.4% for EPICE), while rates across a US Neonatal Network were 19% for moderate to severe NDI.[26] Over time rates of moderate to severe NDI in infants born <28 weeks' gestation from Australia ranged from 28.2% in 1997 to 20.3% in 2005[27] compared with our study rate of 24.8%

A major strength of this study is the use of a standardised protocol, definitions and instruments across a large international population facilitating robust and direct comparisons between countries. This prospective standardisation of data is unique in that it allows the harmonisation of individual patient data rather than the more limited grouped data of meta-analyses[6–8] providing a model for future studies. Outcome data were collected using a parent questionnaire with good diagnostic utility compared with the results of gold standard developmental tests[16 17] and can be a valid, reliable, efficient and cost effective way to assess NDI at 2 years of age.

The use of parent questionnaires can also be a limitation as they do not provide a diagnostic assessment and may overestimate true rates of neurodevelopmental disability in this population[15 17] The PARCA-R has been validated in terms of both diagnostic and clinical utility in the UK, Italy, the Netherlands and New Zealand. However, we have no reason to suspect that it would not perform as well in other European countries. In addition, we were unable to include the verbal composite of PARCA-R as this has not been standardised for many languages. Also around a tenth of questionnaires were returned after 26 months of corrected age. Sensitivity analysis indicated that this had a significant impact on overall but not individual country rates of impairment with the possible exception of Italy where there were late returns for over 15% of the cohort and differences approached significance (p=0.07). As late reporting was not responsible for the difference found between countries, we felt it would be unethical not to include parent completed data. Future studies should

work more closely with parents to ensure timely completion. Response rates varied between countries ranging from 50% to 99%, which can lead to biased estimates of the prevalence of impairment. Similar falling response rates have been noted in recent years in population-based health surveys.[28 29] We found wide variation in rates of moderate to severe NDI between countries both for the crude rates and following adjustment for known risk factors despite similar levels of neonatal morbidity. However, we do not know the level of inherent variation that is residual within these populations and cannot therefore determine what proportion of the variation observed was due to the quality of care provision and treatment of these VPT infants.

In conclusion, this study found wide variation in the rates of moderate to severe NDI, severe NSI and moderate to severe NVC impairment among VPT infants across Europe, most of which persists following adjustment for known maternal, pregnancy and infant factors.

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Acknowledgements The authors would like to thank all the children and families who have participated in the Effective Perinatal Intensive Care in Europe (EPICE) study as well as the health service and school staff who facilitated the data collection and assessments.

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Funding This work was supported by the European Union's Seventh Framework Programme (FP7/2007-2013, No 259882) and the European Union's Horizon 2020 research and innovation programme (No 633724).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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