Variability in Very Preterm Stillbirth and In-Hospital Mortality Across Europe

Elizabeth S. Draper, PhD,[a] Bradley N. Manktelow, PhD,[a] Marina Cuttini, PhD,[b] Rolf F. Maier, MD,[c] Alan C. Fenton, MD,[d] Patrick Van Reempts, MD, PhD,[e,f] Anna-Karin Bonamy, MD, PhD,[g,h] Jan Mazela, MD, PhD,[i] Klaus Bø rch, MD,[j] Corinne Koopman-Esseboom, MD, PhD,[k] Heili Varendi, MD, PhD,[l] Henrique Barros, MD, PhD,[m] Jennifer J. Zeitlin, PhD,[n] on behalf of the EPICE Cohort

abstract

BACKGROUND AND OBJECTIVE: Stillbirth and in-hospital mortality rates associated with very preterm births (VPT) vary widely across Europe. International comparisons are complicated by a lack of standardized data collection and differences in definitions, registration, and reporting. This study aims to determine what proportion of the variation in stillbirth and in-hospital VPT mortality rates persists after adjusting for population demographics, case-mix, and timing of death.

METHODS: Standardized data collection for a geographically defined prospective cohort of VPTs (22^{+0}–31^{+6} weeks gestation) across 16 regions in Europe. Crude and adjusted stillbirth and in-hospital mortality rates for VPT infants were calculated by time of death by using multinomial logistic regression models.

RESULTS: The stillbirth and in-hospital mortality rate for VPTs was 27.7% (range, 19.9%–35.9% by region). Adjusting for maternal and pregnancy characteristics had little impact on the variation. The addition of infant characteristics reduced the variation of mortality rates by approximately one-fifth (4.8% to 3.9%). The SD for deaths <12 hours after birth was reduced by one-quarter, but did not change after risk adjustment for deaths ≥12 hours after birth.

CONCLUSIONS: In terms of the regional variation in overall VPT mortality, over four-fifths of the variation could not be accounted for by maternal, pregnancy, and infant characteristics. Investigation of the timing of death showed that these characteristics only accounted for a small proportion of the variation in VPT deaths. These findings suggest that there may be an inequity in the quality of care provision and treatment of VPT infants across Europe.

[a]Department of Health Sciences, University of Leicester, Leicester, United Kingdom; [b]Clinical Care and Management Innovation Research Area, Bambino Gesù Children's Hospital, Rome, Italy; [c]Children's Hospital, University Hospital, Philipps University Marburg, Marburg, Germany; [d]Newcastle Neonatal Services, Royal Victoria Infirmary, Newcastle, United Kingdom; [e]Department of Neonatology, Antwerp University Hospital, University of Antwerp, Antwerp, Belgium; [f]Flemish Study Centre for Perinatal Epidemiology, Brussels, Belgium; Departments of [g]Medicine Solna and [h]Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden; [i]Department of Neonatology, Poznan University of Medical Sciences, Poznan, Poland; [j]Department of Neonatology, Hvidovre University Hospital, Hvidovre, Denmark; [k]Department of Neonatology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, Netherlands; [l]Department of Pediatrics, University of Tartu, Tartu University Hospital, Tartu, Estonia; [m]EPIUnit Institute of Public Health, University of Porto, Porto, Portugal; and [n]INSERM, Obstetrical, Perinatal and Paediatric Epidemiology Research Team, Centre for Epidemiology and Biostatistics (U1153), Paris-Descartes University, Paris, France

Dr Draper conceptualized and designed the study, acquired the data, developed the analysis strategy, interpreted the data, and drafted the initial manuscript; Dr Zeitlin conceptualized and designed the study, acquired the data, developed the analysis strategy, interpreted the data,

WHAT'S KNOWN ON THIS SUBJECT: The mortality rates associated with very preterm births vary widely across Europe. Direct comparisons of international mortality rates for very preterm infants are complicated by a lack of standardized data collection and differences in definitions, registration, and reporting.

WHAT THIS STUDY ADDS: Variations in stillbirth and in-hospital very preterm mortality rates were reduced by 20% after adjusting for maternal, pregnancy, and infant characteristics. Regional variation was not explained by the variation in the mortality of the earliest deaths.

To cite: Draper ES, Manktelow BN, Cuttini M, et al. Variability in Very Preterm Stillbirth and In-Hospital Mortality Across Europe. *Pediatrics.* 2017;139(4):e20161990

The worldwide burden of preterm birth is increasing.[1] However, since the early 1990s, many improvements in the care of these infants, including routine use of antenatal steroids for women at risk for preterm delivery and surfactant, have led to a dramatic reduction in the associated mortality of these infants, even for those born at <26 weeks' gestation.[2–6] Medical advances in subsequent years have led to a continued reduction in both the mortality and morbidity rates for very preterm infants.[4,7,8] However, wide variations in stillbirth and in-hospital mortality rates for very preterm births (VPTs) have been observed across Europe, with up to twofold differences in these rates between regions.[9–11] These comparisons raise questions about the quality and the equitability of access to perinatal and neonatal care in high-mortality regions or countries.

Using mortality rates as benchmarks for quality of care across countries is contingent on accounting for other sources of variation that affect these rates. Some of the variation can be explained by a lack of standardized data collection and reporting, specifically among the most preterm infants.[12] Worldwide differences in definitions of stillbirths, births, and deaths, access to termination of pregnancy, and registration and reporting of very preterm infants make it difficult to carry out direct comparisons, despite using a standardized approach. In addition, perinatal management of infants at very low gestational ages (GAs) related to unit policy and treatment and ethical concerns around the withholding or withdrawal of care also differs across Europe and impacts on mortality rates.[13–15] Finally, the broad diversity in the demographic characteristics of childbearing women in Europe may affect the patient case-mix.[16,17]

Using the Effective Perinatal Intensive Care in Europe (EPICE) standardized population-based VPT cohort from 19 regions across 11 European countries, this study aims to determine what proportion of the regional variation in stillbirth and in-hospital mortality rates in European regions persists after adjusting for reporting differences in outcomes among VPTs as well as population demographics and case-mix. We additionally investigate regional differences by the timing of death, because causes of death can differ for deaths which occur before, during, or immediately after delivery or on the neonatal unit before discharge.

METHODS

The EPICE birth cohort comprises a geographically defined prospective cohort of outcomes for VPTs between 22^{+0} and 31^{+6} weeks of GA in 19 regions in 11 European countries (Table 1). Regions were selected with respect to geographic and organization diversity (all have at least 1 tertiary center), feasibility (preexisting data systems and expertise), and sample size considerations.

Regional data collection took place by using a standardized protocol between March and July 2011 for 12 months, except in France where data were collected for 6 months, during which there were ~850 000 births in the EPICE regions. Data definitions were agreed on by the EPICE Consortium and data were collected from obstetric and neonatal medical records by the regional teams by using either the EPICE questionnaire or modified regional systems. Ascertainment was validated against birth registers within all hospitals by local teams. Determination of GA was based on the best estimate of the obstetric team caring for the pregnant women. When there were several estimates, GA was based on the following hierarchy: in vitro fertilization treatment, ultrasound based on earliest estimate, last menstrual period, fundal height measurement, and neonatal assessment at birth.

TABLE 1 Participating Countries and Regions in the EPICE Project

European Country	Participating Region(s)
Denmark	Eastern region
Belgium	Flanders
France	Burgundy[a]
	Ile-de-France
	Northern region
Germany	Hesse
	Saarland[a]
Italy	Emilia-Romagna
	Lazio
	Marche[a]
Netherlands	Central and Eastern regions
Poland	Wielkopolska
Portugal	Lisbon
	Northern region
Sweden	Stockholm county
Estonia	Entire country
United Kingdom	East Midlands
	Yorkshire and Humber
	Northern region

[a] Less than 150 VPT births in the study period.

For this analysis, data were excluded for 3 regions with <150 cases (Table 1). Terminations of pregnancy and severe congenital anomalies (Supplemental Information) were also excluded due to the variation in policies regarding the treatment of such cases across the regions.

Outcomes were defined by the type and timing of death or survival to discharge from neonatal care by using the following categories: stillbirth, deaths <12 hours after birth, deaths ≥12 hours to 7 completed days after birth, deaths >7 days after birth, and survivors at discharge from neonatal care. Analysis by GA was performed by using 2-week GA bands to facilitate comparisons, namely 22^{+0}–23^{+6} weeks, 24^{+0}–25^{+6} weeks, 26^{+0}–27^{+6} weeks, 28^{+0}–29^{+6} weeks, and 30^{+0}–31^{+6} weeks.

Maternal and pregnancy characteristics included in the analysis were maternal age, parity, multiple pregnancy, and

pregnancy complications, defined as hypertensive diseases (preeclampsia, eclampsia, and HELLP syndrome), admission to hospital for antepartum hemorrhage after 20^{+0} weeks' gestation, and preterm premature rupture of membranes (PPROM). Infant characteristics were GA at birth, birth weight, sex, multiplicity, and small for GA (SGA; <10th percentile).[18]

Ethics and data protection approvals were provided in each region to fulfill national legislation requirements.

Crude stillbirth, in-hospital mortality, and survival rates are presented using all births as the denominator, with differences between regions in the rates of mortality and of type of mortality tested by using the χ^2 test. Maternal, pregnancy, and infant characteristics are presented as numbers and rates or means with SDs, and the statistical significance of any variation between the regions was tested by using the χ^2 test or analysis of variance as appropriate.

The effects of maternal, pregnancy, and infant factors were investigated by using multinomial logistic regression models. The models simultaneously estimate the probability for each type of death (stillbirth, death <12 hours after birth, and death ≥12 hours after birth) while allowing the magnitude of the effect of each maternal, pregnancy, or infant factor to differ by type of death. This was undertaken first for maternal and pregnancy factors alone (overall mortality) and then for maternal, pregnancy, and infant factors (overall mortality and by timing of death) with associations presented as odds ratios (ORs) with 95% confidence intervals (CIs). Overall and for each type of death, the observed "unadjusted" mortality percentage was calculated for each region. In addition, a standardized mortality ratio was calculated overall and for each type of death for each region from the multinomial logistic model, namely, the ratio of observed to expected number of deaths was calculated by using the estimated risk-specific predicted probabilities from the whole cohort. An "adjusted" mortality percentage was calculated by multiplying the standardized mortality ratio by the appropriate observed death percentage across the whole cohort, both overall and for each type of death for each region. The variation between regions was quantified through the estimation of the SD of the mortality percentages for the regions. Absolute differences between the unadjusted and adjusted mortality percentages overall and for each type of death were then calculated for each region. This data analysis was generated by using SAS software, version 9 (SAS Institute, Inc, Cary, NC).

RESULTS

The EPICE study is comprised of 8888 infants that fulfilled the study criteria in the 16 regions included in this analysis. The overall stillbirth and in-hospital mortality rate for the cohort was 27.7%, with an almost twofold difference across the regions ranging from 19.9% in Stockholm, Sweden to 35.9% in Ile-de-France (Table 2) ($P < .001$). Individual components of the mortality rates showed even wider variation (overall $P < .001$), with stillbirth rates ranging from 11.5% in Stockholm to 24.2% in Ile-de-France; the high stillbirth rate in Ile-de-France largely explains their high overall mortality rate. The variation in hospital mortality for deaths <12 hours showed an over eightfold difference from 1.2% in the Northern region of the United Kingdom to 9.9% in Wielkopolska (Poland). Stockholm had the lowest rates of mortality for deaths occurring between 12 hours and 7 completed days after birth (0.7%). The highest rate for this category of death was 5.4% in Lisbon, Portugal. In-hospital mortality rates for deaths occurring >7 days after birth ranged from 2.3% in Estonia to 6.8% in Lisbon.

Wide variations were observed in maternal and pregnancy characteristics (Table 3), with the proportion of: mothers aged ≥35 years ranging from 15.0% in the Northern region of France to 45.4% in Lazio, Italy ($P < .001$); primiparous mothers ranging from 38.0% in Estonia to 67.6% in Northern Portugal ($P < .001$); and multiple pregnancies from 10.1% in Estonia to 22.1% in Eastern Denmark ($P < .001$). In terms of infant characteristics (Table 4) the mean GA varied between 28.0 weeks in Wielkopolska, Poland and Ile-de-France and 28.8 weeks in Estonia ($P < .001$); and the mean birth weight varied between 1052 g in Ile-de-France and 1234 g in Estonia ($P < .001$). Wide variations were also seen in the proportions of boy infants ($P = .019$) and SGA infants ($P = .043$).

Table 5 presents the proportion of the EPICE cohort at each band of GA (overall $P < .001$). The highest proportions in the lowest gestation band (22–23 weeks) were in Wielkopolska (13.7%) and Ile-de-France (13.2%) compared with only 2.8% in Estonia and 5.6% in Lisbon. Conversely, in the highest GA band (30–31 weeks), proportions varied from 31.4% in the Eastern region of Denmark to 45.2% in Estonia.

GA at birth has a major impact on the mortality rates of a region (Fig 1 A–E). Overall cohort survival by GA band was 4.2% at 22 to 23 weeks (survivors all 23 weeks), 44.6% at 24 to 25 weeks, 70.5% at 26 to 27 weeks, 84.9% at 28 to 29 weeks, and 91.0% at 30 to 31 weeks. Variation in stillbirth and in-hospital mortality rates was greatest at the lowest GA band (22–23 weeks) in terms of absolute mortality rates, but continued across all GAs in terms of the variation in relative rates, with a threefold range in stillbirth rates at 22 to 23 weeks

TABLE 2 In-Hospital Outcomes by Time of Death or Survival for VPTs Between 22^{+0} and 31^{+6} Weeks of Gestation by European Region: EPICE Cohort 2011 to 2012

	Stillbirth		Timing of Death Before Discharge								Survival to Discharge		Total
			<12 h		≥12 to <48 h		≥48 h to ≤7 d		>7 d				
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*
Belgium: Flanders	154	17.1	42	4.7	12	1.3	14	1.6	28	3.1	651	72.3	901
Denmark: Eastern	62	15.2	28	6.9	9	2.2	6	1.5	17	4.2	286	70.1	408
Estonia	26	14.7	3	1.7	1	0.6	3	1.7	4	2.3	140	79.1	177
France: Northern	68	17.9	17	4.5	1	0.3	11	2.9	7	1.8	275	72.6	379
France: Ile-de-France	282	24.2	63	5.4	5	0.4	29	2.5	38	3.3	746	64.1	1163
Germany: Hesse	81	11.9	31	4.6	6	0.9	12	1.8	20	2.9	528	77.9	678
Italy: Lazio	106	15.8	24	3.6	18	2.7	14	2.1	35	5.2	472	70.6	669
Italy: Emilia	50	10.1	11	2.2	12	2.4	12	2.4	17	3.4	391	79.3	493
Netherlands: Eastern and Central[a]	66	14.6	16	3.5	12	2.7	10	2.2	19	4.2	329	72.8	452
Poland: Wielkopolska	67	18.4	36	9.9	9	2.5	6	1.6	11	3.0	236	64.7	365
Portugal: Northern	63	18.3	9	2.6	6	1.7	7	2.0	14	4.1	246	71.3	345
Portugal: Lisbon	79	15.3	14	2.7	18	3.5	10	1.9	35	6.8	360	69.8	516
United Kingdom: Northern[a]	79	15.9	6	1.2	7	1.4	5	1.0	20	4.0	380	76.5	497
United Kingdom: East Midlands	118	17.2	30	4.4	10	1.5	9	1.3	12	1.7	507	73.9	686
United Kingdom: Yorkshire and Humber	135	15.7	28	3.3	13	1.5	9	1.0	38	4.4	638	74.1	861
Sweden: Stockholm	34	11.5	9	3.0	0	0.0	2	0.7	14	4.7	237	80.1	296
All regions	1470	16.5	367	4.1	139	1.6	159	1.8	328	3.7	6422	72.3	8886

[a] One infant with unknown outcome.

TABLE 3 Maternal and Pregnancy Characteristics for VPTs Between 22^{+0} and 31^{+6} Weeks of Gestation by European Region: EPICE Cohort 2011 to 2012

	No. of Mothers	Mothers Aged ≥35 y		Primiparous		Hypertensive Disease[a]		PPROM		Multiple Pregnancy	
	N	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Belgium: Flanders	737	142	19.3	411	55.8	108	14.7	173	23.5	157	21.3
Denmark: Eastern	330	80	24.2	186	56.4	36	10.9	64	19.4	73	22.1
Estonia	158	55	34.8	60	38.0	24	15.2	51	32.3	16	10.1
France: Northern	321	48	15.0	163	50.8	53	16.5	70	21.8	55	17.1
France: Ile-de-France	992	250	25.2	489	49.3	180	18.1	241	24.3	161	16.2
Germany: Hesse	559	159	28.4	329	58.9	75	13.4	150	26.8	113	20.2
Italy: Lazio	562	255	45.4	313	55.7	52	9.3	137	24.4	107	19.0
Italy: Emilia	418	172	41.1	262	62.7	64	15.8	81	19.4	72	17.2
Netherlands: Eastern and Central	387	76	19.6	245	63.3	64	16.5	80	20.7	63	16.3
Poland: Wielkopolska	328	64	19.5	154	47.0	24	7.3	94	28.7	37	11.3
Portugal: Northern	299	74	24.7	202	67.6	54	18.1	61	20.4	46	15.4
Portugal: Lisbon	439	129	29.4	236	53.8	74	16.9	114	26.0	75	17.1
United Kingdom: Northern	436	78	17.9	187	42.9	30	6.9	100	22.9	64	14.7
United Kingdom: East Midlands	601	113	18.8	300	49.9	88	14.6	123	20.5	86	14.3
United Kingdom: Yorkshire and Humber	769	151	19.6	378	49.2	95	12.4	187	24.3	87	11.3
Sweden: Stockholm	254	92	36.2	141	55.5	50	19.7	50	19.7	41	16.1
All regions	7590	1938	25.5	4056	53.4	1071	14.1	1776	23.4	1253	16.5
P[b]		<.001		<.001		<.001		.004		<.001	

[a] Preeclampsia, eclampsia, or HELLP syndrome

[b] *P* value for overall difference between the regions.

GA (29.3% in Hesse, Germany to 85.7% in the Northern region of Portugal) and at 29 to 31 weeks GA (3.4% in Emilia Romagna, Italy to 9.7% in Ile-de-France). Detailed tables by GA group and region are provided as Supplemental Tables 7–11.

Adjusted ORs with 95% CIs are presented in Table 6 for maternal, pregnancy, and infant characteristics by outcome. Very preterm stillbirths

TABLE 4 Infant Characteristics for VPTs Between 22^{+0} and 31^{+6} Weeks of Gestation by European Region: EPICE Cohort 2011 to 2012

	No. of Infants	GA at Birth, wk		Birth Weight, g		Boy		Twin or Higher Order		SGA[a]	
	N	Mean	SD	Mean	SD	*N*	%	*N*	%	*N*	%
Belgium: Flanders	901	28.5	2.8	1178	458	510	56.6	321	35.6	280	31.1
Denmark: Eastern	408	28.1	2.7	1079	450	214	52.5	151	37.0	167	40.9
Estonia	177	28.8	2.4	1234	418	87	49.2	35	19.8	59	33.3
France: Northern	379	28.1	2.8	1070	418	210	55.4	113	29.8	142	37.5
France: Ile-de-France	1163	28.0	2.9	1052	427	603	51.8	332	28.5	420	36.1
Germany: Hesse	678	28.3	2.8	1132	431	357	52.7	232	34.2	250	36.9
Italy: Lazio	669	28.3	2.8	1121	434	341	51.0	214	32.0	227	33.9
Italy: Emilia	493	28.5	2.8	1149	465	233	47.3	147	29.8	161	32.7
Netherlands: Eastern and Central	453	28.5	2.7	1133	456	230	50.8	129	28.5	166	36.6
Poland: Wielkopolska	365	28.0	3.0	1123	500	197	54.0	74	20.3	110	30.1
Portugal: Northern	345	28.4	2.6	1071	392	192	55.7	92	26.7	137	39.7
Portugal: Lisbon	516	28.4	2.6	1088	387	298	57.8	152	29.5	179	34.7
United Kingdom: Northern	498	28.3	2.7	1116	432	289	58.0	126	25.3	168	33.7
United Kingdom: East Midlands	686	28.6	2.7	1161	435	354	51.6	171	24.9	236	34.4
United Kingdom: Yorkshire and Humber	861	28.4	2.6	1127	403	476	55.3	179	20.8	291	33.8
Sweden: Stockholm	296	28.3	2.7	1156	459	158	53.4	83	28.0	102	34.5
Overall	8888	28.3	2.8	1120	437	4749	53.4	2551	28.7	3095	34.8
P[b]		<.001		<.001		.019		<.001		.043	

[a] Less than 10th percentile birth weight.

[b] *P* value for overall difference between the regions.

TABLE 5 Numbers of VPTs (22^{+0}–31^{+6} Weeks of Gestation) by European Region, Stratified by GA: EPICE Cohort 2011 to 2012

	GA at Birth									
	22^{+0}–23^{+6} wk		24^{+0}–25^{+6} wk		26^{+0}–27^{+6} wk		28^{+0}–29^{+6} wk		30^{+0}–31^{+6} wk	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Belgium: Flanders	78	8.7	144	12.7	114	12.7	203	22.5	392	43.5
Denmark: Eastern	44	10.8	48	11.8	90	22.1	98	24.0	128	31.4
Estonia	5	2.8	23	13.0	36	20.3	33	18.6	80	45.2
France: Northern	42	11.1	46	12.1	76	20.1	76	20.1	139	36.7
France: Ile-de-France	153	13.2	153	13.2	189	16.3	259	22.3	409	35.2
Germany: Hesse	58	8.6	94	13.9	120	17.7	145	21.4	261	38.5
Italy: Lazio	69	10.3	85	12.7	97	14.5	164	24.5	254	38.0
Italy: Emilia	47	9.5	43	8.7	90	18.3	99	20.1	214	43.4
Netherlands: Eastern and Central	37	8.2	54	11.9	87	19.2	89	19.6	186	41.1
Poland: Wielkopolska	50	13.7	49	13.4	59	16.2	71	19.5	136	37.3
Portugal: Northern	28	8.1	31	9.0	78	22.6	82	23.8	126	36.5
Portugal: Lisbon	29	5.6	67	13.0	109	21.1	125	24.2	186	36.0
United Kingdom: Northern	38	7.6	77	15.5	77	15.5	131	26.3	175	35.1
United Kingdom: East Midlands	56	8.1	76	11.1	102	14.9	160	23.3	292	42.6
United Kingdom: Yorkshire and Humber	58	6.8	117	13.6	140	16.3	217	25.2	329	38.2
Sweden: Stockholm	27	9.1	45	15.2	38	12.8	84	28.4	102	34.5
Overall	819	9.2	1122	12.6	1502	16.9	2036	22.9	3409	38.4

and infants who died after ≥12 hours of neonatal care were significantly less likely to have a primiparous mother than very preterm survivors. Similarly, VPTs born to mothers with PPROM or mothers identified as having a hypertensive pathology (preeclampsia, eclampsia, or HELLP syndrome) had less risk of stillbirth or death after ≥12 hours of life. In addition to the expected inverse relationship between all poor outcomes and increasing GA, stillbirths were less likely to be from a multiple pregnancy compared with survivors and being SGA was associated with stillbirth or death regardless of timing. There were significant differences for all maternal, pregnancy, and infant characteristics presented

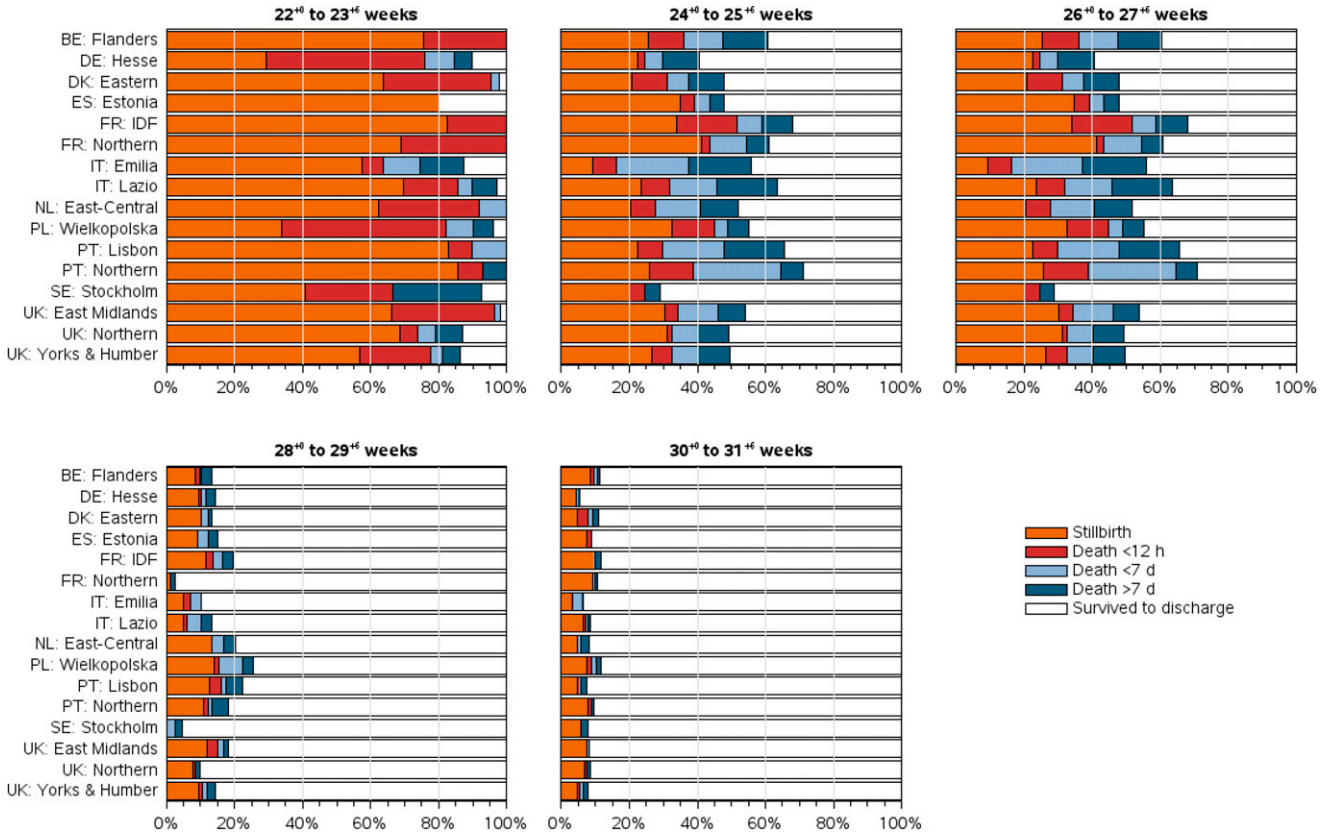

FIGURE 1
Outcome by GA group for VPTs between 22^{+0} and 31^{+6} weeks of gestation by European region: EPICE cohort 2011 to 2012.

across the 3 outcomes apart from maternal age.

Variation in the overall stillbirth and in-hospital mortality rates by region reduced little after adjusting for maternal and pregnancy factors from a SD of 4.8% for the distribution of unadjusted regional mortality rates (range, 20.0%–35.9%) to a SD of 4.7% (range, 20.5%–36.6%). However, additional adjustment for infant factors reduced the SD for the distribution of regional mortality rates to 3.9% (range, 20.0%–33.7%), largely due to GA. After adjusting for maternal, pregnancy, and infant factors, the SD of mortality rates by timing of death reduced by approximately one-tenth from 3.3% (range, 10.1%–24.3%) to 3.0% (range, 10.6%–22.0%) for stillbirths; by approximately one-quarter from 2.1% (range, 1.2%–9.9%) to 1.5% (range, 1.3%–7.8%) for deaths at <12 hours of age; and was 2.1% both before adjustment (range, 4.5%–12.2%) and after adjustment (range, 4.6%–11.4%) for deaths at ≥12 hours of age. The differences between regions all remained statistically significant ($P < .001$).

The impact of maternal, pregnancy, and infant characteristics on the timing of death for each region are shown in Fig 2, which illustrates the absolute differences in stillbirth and in-hospital mortality rates between the overall rates for the total cohort and the rates for each region. Adjustment for these characteristics changed the mortality estimates for Ile-de-France, Wielkopolska, and Estonia for stillbirths and deaths at <12 hours but had little effect on the UK region of Yorkshire and Humber for any mortality outcome. Deaths at ≥12 hours showed the smallest variation after risk adjustment for maternal, pregnancy, and infant characteristics.

DISCUSSION

This analysis identified wide variations in very preterm stillbirth and in-hospital mortality rates across Europe in the EPICE cohort from 2011 to 2012 by using standardized data collection procedures after accounting for population demographics, case mix, and timing of death and confirms previous findings.[9] We show that these variations are evident for all outcomes, although variation is greatest (in relative terms) for the earliest deaths, predominantly those occurring <12 hours after birth. Although birth registration differences or policies for ascribing whether an infant is recorded as a stillbirth or neonatal death may account for some of the variation for the earliest GAs,[12] this is not the case for births at later gestational ages (≥27 weeks), where GA plays a lesser role in the determination of potential

TABLE 6 Adjusted ORs for Maternal, Pregnancy, and Infant Characteristics by Timing of Death Compared With Survival to Discharge for VPTs Between 22^{+0} and 31^{+6} Weeks of Gestation: EPICE Cohort 2011 to 2012

	Stillbirth		Neonatal Death <12 h After Birth		Neonatal Death ≥12 h After Birth		
	OR	95% CI	OR	95% CI	OR	95% CI	*P*
Mother's age, y							.29
<20	1.30	0.91–1.85	1.37	0.76–2.45	0.97	0.59–1.57	
20–34	Referent		Referent		Referent		
≥35	0.95	0.79–1.13	0.75	0.55–1.02	1.07	0.87–1.31	
Parity							<.001
0	0.79	0.67–0.93	0.80	0.61–1.05	0.77	0.64–0.94	
1–2	Referent		Referent		Referent		
≥3	1.10	0.83–1.44	1.49	0.96–2.31	1.12	0.81–1.55	
Hypertensive pathology							<.001
No	Referent		Referent		Referent		
Yes	0.17	0.12–0.23	0.46	0.26–0.82	0.79	0.59–1.07	
PPROM							<.001
No	Referent		Referent		Referent		
Yes	0.37	0.30–0.46	0.77	0.57–1.02	0.74	0.60–0.93	
Sex of infant							.019
Girl	Referent		Referent		Referent		
Boy	0.89	0.76–1.03	1.21	0.94–1.55	1.16	0.97–1.39	
GA at birth							<.001
22–23 wk	327.06	220.48–485.15	970.99	538.10–>999	107.17	65.28–175.93	
24–25 wk	10.27	8.23–12.81	29.92	17.97–49.83	25.78	19.05–34.87	
26–27 wk	3.00	2.42–3.71	5.50	3.14–9.66	8.58	6.35–11.60	
28–29 wk	1.46	1.17–1.82	2.36	1.29–4.30	2.78	2.00–3.86	
30–31 wk	Referent		Referent		Referent		
Multiplicity							<.001
Singleton	Referent		Referent		Referent		
Multiple	0.32	0.26–0.40	0.76	0.57–1.03	0.88	0.72–1.08	
<10th birth-weight percentile							<.001
No	Referent		Referent		Referent		
Yes	4.67	3.99–5.50	1.68	1.24–2.26	1.66	1.36–2.04	

viability. Nevertheless, because the highest levels of variation are found for the deaths that occur closest to birth, it suggests that unit and regional policy differences may account for a proportion of this difference, possibly representing the full spectrum of interventions for compassionate and palliative care across regions. This difference in policies may contribute to the variation seen in the later deaths because more proactive initiation of treatment may lead to increased survival in those infants who were previously thought to be at highest risk of mortality.[19]

To assess the full picture of outcomes associated with VPTs, it is important to investigate outcomes for the total cohort, including all stillbirths, intrapartum, and labor ward deaths as well as deaths on neonatal units to reduce the selection bias introduced by management policies.[20] One example of this is the variation in the amount of infants admitted to a unit for comfort care when early death is anticipated, a policy adopted by the Polish region of Wielkopolska, whereas other regions may allow such deaths to occur in the delivery suite and, in some circumstances, they may fail to appear in official statistics. In many countries, decision-making about potential viability takes place in the maternity unit, reflecting differences in obstetric and perinatal practices in addition to health system factors and the impact of cultural attitudes.

A number of maternal and pregnancy characteristics are known to be associated with rates of very preterm delivery and the subsequent risk of mortality. In this analysis, we have noted both demographic variations in terms of maternal age, proportion of primiparous mothers, and pregnancy complications (hypertensive pathology and PPROM). However, despite variations in these characteristics across the regions, they had a minimal effect on the regional variation in VPT mortality rates.

Similarly, infant characteristics that are known to have an association with mortality were investigated, and variations in the proportion of VPTs that were boys, from multiple births, or had fetal growth restriction were noted across the regions. When infant characteristics were added into the risk adjustment model, the variation in overall stillbirth and in-hospital mortality rates across the study regions reduced by nearly one-quarter (23.3%), indicating the lack

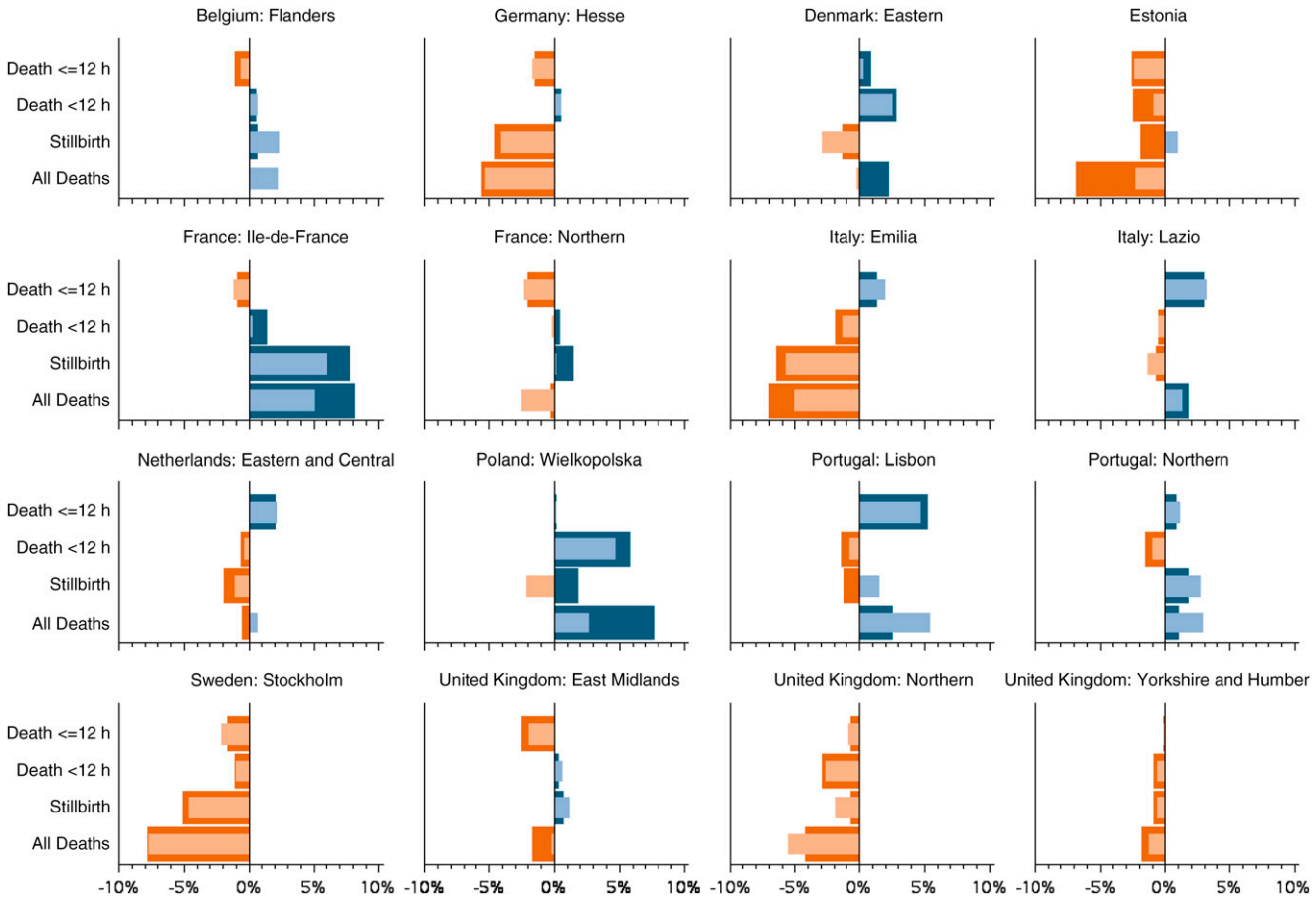

FIGURE 2

Difference in absolute mortality rate from overall mortality rate unadjusted (dark shade) and adjusted for maternal, pregnancy, and infant characteristics (light shade) for VPTs between 22^{+0} and 31^{+6} weeks of gestation by European region: EPICE cohort 2011 to 2012. Values to the right (blue) represent mortality rates that were higher than the overall average and values to the left (amber) represent mortality rates that were lower than the overall average.

of homogeneity in the populations of infants in the different regions.

Investigation of the effect of adjusting for maternal, pregnancy, and infant characteristics by the timing of death shows that interregional variation persists at all 3 specified timings. This is contrary to the findings of the EXPRESS study in Sweden,[11] which concluded that in the most extreme preterm infants, any regional differences were established <12 hours after birth, suggesting they could be related to variations in immediate perinatal practices. The continued wide variation in mortality for infants ≥12 hours of age in the EPICE cohort could indicate that there is variation in the quality, access, and provision of neonatal care across Europe. The profile of VPT is changing over time, with increasing numbers of earlier gestation infants, partly due to increasing iatrogenic early delivery as neonatal care has improved.[21–23] The wide variation in mortality rates seen in the deaths at ≥12 hours of age may be due to the increasing complexity of these extremely preterm births.

Strengths of the Study

This study used a population-based prospective cohort study design with standardized data collection and definitions. Active validation of regional case ascertainment was carried out to ensure inclusion of all cases that fulfilled the study criteria, irrespective of local registration criteria for births and deaths. All terminations of pregnancy and major congenital anomalies were excluded to allow for other differences in the legislative practices between countries, although differences in perinatal management and policies for any other congenital anomaly may still have had an impact on our results. Our main analysis was carried out by using the timing of the death rather than admissions to the NICU, thus reducing the impact of the variations in unit and regional policies with respect to the treatment of this group.[19]

Limitations of the Study

There is no standardized method of ascertainment of socioeconomic status across Europe that can be derived from medical records[24] and,

therefore, no adjustment has been made for this particular population characteristic, which is known to be associated with preterm birth. However, although there is a doubling of the risk of VPT between the least and most deprived groups in populations,[25] variations in the outcome of VPTs after admission to neonatal care do not appear to be explained by socioeconomic differences.[26,27]

Although the calculation of expected date of delivery for the vast majority of births is now assessed by ultrasound measurement, this is not always the case. In addition, there is variation in the dating formulae used for sonographic estimation of GA between regions,[28] which could lead to systematic variation. In this study, we have used the best estimate for GA based on ultrasound as the gold standard where possible and have identified a hierarchy for the calculation of GA when a number of estimates were provided.

CONCLUSIONS

The aim of this study was to determine what proportion of the regional variations in stillbirth and in-hospital mortality rates in European regions persists after adjusting for population demographics and case mix. Over 75% of the regional variation could not be accounted for by these factors. Investigation of the timing of death showed that approximately one-tenth of the variation in the stillbirth rate was accounted for by maternal, pregnancy, and infant characteristics. However, one-quarter of the variation in the mortality rate for deaths occurring <12 hours after birth, but almost none of the variation in the mortality rate for deaths occurring ≥12 hours after birth, seems to be explained by these same characteristics. This finding suggests that there may be an inequity in the quality of care provision and treatment of very preterm infants across Europe.

ACKNOWLEDGMENTS

EPICE Research Group: Flanders, Belgium: H. Cammu, E. Martens, G. Martens, and P. Van Reempts; Eastern region, Denmark: K. Boerch, A. Hasselager, L. Huusom, O. Pryds, and T. Weber; Estonia: L. Toome and H. Varendi; Burgundy, Ile-de France, and Northern region, France: P.Y. Ancel, B. Blondel, M. Bonet (Research Coordinator; INSERM), A. Burguet, J.B. Gouyon, P.H. Jarreau, P. Truffert, and J. Zeitlin (Project Leader; INSERM); Hesse, Germany: R.F. Maier, B. Misselwitz, and S. Schmidt; Saarland, Germany: Emilia Romagna, Italy: L. Gortner; D. Baronciani, G. Gargano; Lazio, Italy: R. Agostino, D. DiLallo, and F. Franco; Le Marche, Italy: V. Carnielli, M. Cuttini, and I. Croci; Eastern and Central regions, Netherlands: C. Hukkelhoven, M. Hulscher, L. Kollée, C. Koopman-Esseboom, and A. Van Heijst; Wielkopolska, Poland: J. Gadzinowski and J. Mazela; Lisbon and Tagus Valley, Portugal: L.M. Graça and Md.C. Machado; Northern region, Portugal: H. Barros, M.R.G. Carrapato, and T. Rodrigues; Stockholm, Sweden: A.K. Bonamy, M. Norman, and E. Wilson; East Midlands and Yorkshire and Humber, United Kingdom: E. Boyle, E.S. Draper, and B.N. Manktelow; and Northern region, United Kingdom: A.C. Fenton and D.W.A. Milligan.

ABBREVIATIONS

CI: confidence interval
EPICE: Effective Perinatal Intensive Care in Europe
GA: gestational age
OR: odds ratio
PPROM: preterm premature rupture of membranes
SGA: small for gestational age
VPT: very preterm birth

and revised the manuscript; Dr Manktelow designed the analysis strategy, carried out the data analysis, and revised the manuscript; Drs Cuttini, Maier, Fenton, Van Reempts, Bonamy, Mazela, Boerch, Koopman-Esseboom, and Varendi designed and organized the study, acquired the data, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2016-1990

Accepted for publication Jan 17, 2017

Address correspondence to Elizabeth S. Draper, PhD, Department of Health Sciences, College of Medicine, Biological Sciences and Psychology, University of Leicester, Centre for Medicine, University Rd, Leicester LE1 7RH. E-mail: msn@le.ac.uk

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This work was supported by the European Union's Seventh Framework Programme ([FP7/2007-2013]) under grant agreement 259882. Additional funding was received in the following regions: France (French Institute of Public Health Research/Institute of Public Health and its partners the French Health Ministry, the National Institutes of Health and Medical Research, the National Institute of Cancer, and the National Solidarity Fund for Autonomy; grant ANR-11-EQPX-0038 from the National Research Agency through the French Equipex Program of Investments in the Future; and the PremUp Foundation); Poland (2012–2015 allocation of funds for international projects from the Polish Ministry of Science and Higher Education); Sweden (Stockholm County Council [ALF project and Clinical Research Appointment (Anna-Karin Bonamy)] and by the Department of Neonatal Medicine, Karolinska University Hospital); and the United Kingdom

(funding for the Neonatal Survey from Neonatal Networks for East Midlands and Yorkshire and Humber regions). The funders had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet*. 2012;379(9832):2162–2172
2. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*. 2006;(3):CD004454
3. Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev*. 2001; (2):CD000510
4. Costeloe KL, Stacey F, Hennessy E et al. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ*. 2012;345:e7976
5. Field DJ, Dorling JS, Manktelow BN, Draper ES. Survival of extremely premature babies in a geographically defined population: prospective cohort study of 1994-9 compared with 2000-5. *BMJ*. 2008;336(7655):1221–1223
6. Patel RM, Kandefer S, Walsh MC, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Causes and timing of death in extremely premature infants from 2000 through 2011. *N Engl J Med*. 2015;372(4):331–340
7. McCall EM, Alderdice F, Halliday HL et al. Interventions to prevent hypothermia at birth in preterm and/or low birthweight infants. *Cochrane Database Syst Rev*. 2010;(3):CD004210
8. Stoll BJ, Hansen NI, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA*. 2015;314(10):1039–1051
9. Draper ES, Zeitlin J, Fenton AC, et al; MOSAIC research group. Investigating the variations in survival rates for very preterm infants in 10 European regions: the MOSAIC birth cohort. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(3):F158–F163
10. Zeitlin J, Draper ES, Kollée L, et al; MOSAIC research group. Differences in rates and short-term outcome of live births before 32 weeks of gestation in Europe in 2003: results from the MOSAIC cohort. *Pediatrics*. 2008;121(4). Available at: www.pediatrics.org/cgi/content/full/121/4/e936
11. Serenius F, Sjörs G, Blennow M, et al; EXPRESS study group. EXPRESS study shows significant regional differences in 1-year outcome of extremely preterm infants in Sweden. *Acta Paediatr*. 2014;103(1):27–37
12. Smith L, Draper ES, Manktelow BN, Pritchard C, Field DJ. Comparing regional infant death rates: the influence of preterm births <24 weeks of gestation. *Arch Dis Child Fetal Neonatal Ed*. 2013;98(2):F103–F107
13. Draper ES. Evaluating and comparing neonatal outcomes. *Arch Dis Child Fetal Neonatal Ed*. 2010;95(3):F158–F159
14. Kollée LA, Cuttini M, Delmas D, et al; MOSAIC Research group. Obstetric interventions for babies born before 28 weeks of gestation in Europe: results of the MOSAIC study. *BJOG*. 2009;116(11):1481–1491
15. Larroque B, Bréart G, Kaminski M, et al; Epipage study group. Survival of very preterm infants: Epipage, a population based cohort study. *Arch Dis Child Fetal Neonatal Ed*. 2004;89(2):F139–F144
16. Delnord M, Blondel B, Zeitlin J. What contributes to disparities in the preterm birth rate in European countries? *Curr Opin Obstet Gynecol*. 2015;27(2):133–142
17. Zeitlin J, Papiernik E, Bréart G, Draper E, Kollée L; MOSAIC Research Group. Presentation of the European project models of organising access to intensive care for very preterm births in Europe (MOSAIC) using European diversity to explore models for the care of very preterm babies. *Eur J Obstet Gynecol Reprod Biol*. 2005;118(2):272–274
18. Mikolajczyk RT, Zhang J, Betran AP, et al. A global reference for fetal-weight and birthweight percentiles. *Lancet*. 2011;377(9780):1855–1861
19. Rysavy MA, Li L, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Between-hospital variation in treatment and outcomes in extremely preterm infants. *N Engl J Med*. 2015;372(19):1801–1811
20. Evans DJ, Levene MI. Evidence of selection bias in preterm survival studies: a systematic review. *Arch Dis Child Fetal Neonatal Ed*. 2001;84(2):F79–F84
21. Barros FC, Vélez MP. Temporal trends of preterm birth subtypes and neonatal outcomes. *Obstet Gynecol*. 2006;107(5):1035–1041
22. Ananth CV, Joseph KS, Oyelese Y, Demissie K, Vintzileos AM. Trends in preterm birth and perinatal mortality among singletons: United States, 1989 through 2000. *Obstet Gynecol*. 2005;105(5 pt 1):1084–1091
23. Lisonkova S, Hutcheon JA, Joseph KS. Temporal trends in neonatal outcomes following iatrogenic preterm delivery. *BMC Pregnancy Childbirth*. 2011;11:39
24. Zeitlin J, Mortensen L, Prunet C, et al; Euro-Peristat Scientific Committee. Socioeconomic inequalities in stillbirth rates in Europe: measuring the gap using routine data from the Euro-Peristat Project. *BMC Pregnancy Childbirth*. 2016;16:15
25. Smith LK, Draper ES, Manktelow BN, Field DJ. Socioeconomic inequalities in survival and provision of neonatal care: population based study of very preterm infants [published correction

appears in *BMJ*. 2009:339; b5196]. *BMJ*. 2009;339:b4702

26. Rogowski JA, Horbar JD, Staiger DO, Kenny M, Carpenter J, Geppert J. Indirect vs direct hospital quality indicators for very low-birth-weight infants. *JAMA*. 2004;291(2):202–209
27. Hayter MA, Anderson L, Claydon J, et al; Canadian Neonatal Network. Variations in early and intermediate neonatal outcomes for inborn infants admitted to a Canadian NICU and born of hypertensive pregnancies. *J Obstet Gynaecol Can*. 2005;27(1):25–32
28. Simic M, Amer-Wåhlin I, Maršál K, Källén K. Effect of various dating formulae on sonographic estimation of gestational age in extremely preterm infants. *Ultrasound Obstet Gynecol*. 2012;40(2):179–185

Variability in Very Preterm Stillbirth and In-Hospital Mortality Across Europe

Elizabeth S. Draper, Bradley N. Manktelow, Marina Cuttini, Rolf F. Maier, Alan C. Fenton, Patrick Van Reempts, Anna-Karin Bonamy, Jan Mazela, Klaus B?rch, Corinne Koopman-Esseboom, Heili Varendi, Henrique Barros, Jennifer J. Zeitlin and on behalf of the EPICE Cohort

Pediatrics 2017;139;
DOI: 10.1542/peds.2016-1990 originally published online March 24, 2017;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Variability in Very Preterm Stillbirth and In-Hospital Mortality Across Europe

Elizabeth S. Draper, Bradley N. Manktelow, Marina Cuttini, Rolf F. Maier, Alan C. Fenton, Patrick Van Reempts, Anna-Karin Bonamy, Jan Mazela, Klaus B?rch, Corinne Koopman-Esseboom, Heili Varendi, Henrique Barros, Jennifer J. Zeitlin and on behalf of the EPICE Cohort

Pediatrics 2017;139;
DOI: 10.1542/peds.2016-1990 originally published online March 24, 2017;