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Differences in Rates and Short-term Outcome of Live Births Before 32 Weeks of Gestation in Europe in 2003: Results From the MOSAIC Cohort

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What's Known on This Subject

Very preterm birth accounts for a large proportion of perinatal deaths and impairments in childhood, but comparative population-based data on the mortality and morbidity of very preterm babies are not readily available.

What This Study Adds

Using a common protocol, this study finds large differences in very preterm mortality and neurologic and respiratory morbidity between European regions with similar standards of living and healthcare provision raising questions about variability in treatment decisions and population characteristics.

ABSTRACT

OBJECTIVES. Advances in perinatal medicine increased survival after very preterm birth in all countries, but comparative population-based data on these births are not readily available. This analysis contrasts the rates and short-term outcome of live births before 32 weeks of gestation in 10 European regions.

METHODS. The Models of Organizing Access to Intensive Care for Very Preterm Births (MOSAIC) study collected prospective data on all very preterm births in 10 European regions covering 494 463 total live births in 2003. The analysis sample was live births between 24 and 31 weeks of gestation without lethal congenital anomalies ($N = 4908$). Outcomes were rates of preterm birth, in-hospital mortality, intraventricular hemorrhage grades III and IV or cystic periventricular leukomalacia and bronchopulmonary dysplasia. Mortality and morbidity rates were standardized for gestational age and gender.

RESULTS. Live births between 24 and 31 weeks of gestation were 9.9 per 1000 total live births with a range from 7.6 to 13.0 in the MOSAIC regions. Standardized mortality was doubled in high versus low mortality regions (18%–20% vs 7%–9%) and differed for infants ≤ 28 weeks of gestation as well as 28 to 31 weeks of gestation. Morbidity among survivors also varied (intraventricular hemorrhage/periventricular leukomalacia ranged from 2.6% to $\leq 10\%$ and bronchopulmonary dysplasia from 10.5% to 21.5%) but differed from mortality rankings. A total of 85.2 very preterm infants per 10 000 total live births were discharged from the hospital alive with a range from 64.1 to 117.1; the range was 10 to 31 per 10 000 live births for infants discharged with a diagnosis of neurologic or respiratory morbidity.

CONCLUSIONS. Very preterm mortality and morbidity differed between European regions, raising questions about variability in treatment provided to these infants. Comparative follow-up studies are necessary to evaluate the impact of these differences on rates of cerebral palsy and other disabilities associated with preterm birth.

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Key Words

very preterm birth, neonatal mortality, neurologic morbidity, bronchopulmonary dysplasia

Abbreviations

BPD—bronchopulmonary dysplasia
MOSAIC—Models of Organizing Access to Intensive Care for Very Preterm Births
GA—gestational age
IVH—intraventricular hemorrhage
PVL—cystic periventricular leukomalacia

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INFANTS WHO ARE BORN very preterm constitute approximately one third of deaths in the perinatal period, and survivors are at high risk for long-term disabling impairments. Previous studies found that between 5% and 10% of infants who were born at <32 weeks of gestation and discharged alive from hospital developed cerebral palsy¹⁻⁴ and that infants

without severe disabilities face twofold or greater risks for developmental, cognitive, and behavioral difficulties in childhood.^{5,6}

Medical advances in neonatal intensive care coupled with programs to regionalize perinatal care have improved survival after very preterm birth, leading to increases in the numbers of infants who are discharged from the hospital after very preterm birth. In some regions, higher survival has been accompanied by increases in short-term morbidity, such as brain hemorrhaging and bronchopulmonary dysplasia (BPD).⁷⁻⁹ In others, mortality and morbidity both have decreased, so although more infants are at risk, each infant's individual risk for morbidity is lower.¹⁰⁻¹³ On a population level, the evidence for how these evolutions affect rates of impairment is not concordant. In some regions, rates of cerebral palsy have risen in parallel with increased survival among very preterm infants,^{2,14} whereas in others, the same evolutions in practices and survival did not significantly affect cerebral palsy rates.^{3,15} Almost everywhere, however, the proportion of cerebral palsy cases associated with very preterm birth has risen.^{2,3,14,15}

Despite the public health significance of very preterm infants, data for assessing the evolution of their characteristics, mortality, and short-term morbidity are not readily available. There is wide variability in inclusion criteria and completeness in civil and birth registers for very preterm births, and these sources do not often contain information on morbidity.¹⁶ Studies based solely on infants who are admitted to neonatal units are not comparable because of selection biases linked to the participating units and to the exclusion of infants that are not resuscitated at birth. Furthermore, many studies are limited to the use of birth weight as an inclusion criterion (<1500 g or <1000 g), complicating comparisons with studies that are based on gestational age (GA).

The Models of Organizing Access to Intensive Care for Very Preterm Births (MOSAIC) study on models of perinatal care and health outcomes of very preterm infants in Europe collected data using a common protocol on population-based cohorts of very preterm infants from 10 regions covering half a million total births in 2003. One of the study's principal aims was to assess the variability in mortality and short-term morbidity after very preterm birth in European regions.

METHODS

The MOSAIC study included all stillbirths and live births from 22⁺⁰ weeks to 31⁺⁶ weeks of gestation in 10 regions in 9 European countries in 2003. Participating regions were Flanders in Belgium, the Eastern Region of Denmark, 6 of 8 districts in the Ile-de-France region of France, Hesse in Germany, Lazio in Italy, the Central and Eastern regions of the Netherlands, Wielkopolska and Lubuskie in Poland, the Northern region of Portugal, and the Northern and Trent regions of the United Kingdom. The MOSAIC regions covered between 30 000 and 65 000 live births in 2003, with the exception of the larger French region (135 000 births). Regions represented different organizational models of perinatal care identified in a previous European collaboration.¹⁷ The study's other objectives were to describe

the organization of maternity and neonatal units¹⁸ and to assess perinatal health outcome with respect to the organization of perinatal care.

The study was conducted on all births from January 1 to December 31, 2003, with the exception of the Ile-de-France region, where births were included from February 1 to August 31, 2003. GA was based on the best obstetric assessment, using information on last menstrual period and ultrasound measures. Ultrasound scans for dating pregnancies are part of routine antenatal care in the MOSAIC regions. Infants were followed until discharge from the hospital or into long-term care or death.

The MOSAIC consortium selected data items with common definitions to be collected on each infant from information available in medical charts using a structured questionnaire. Data were abstracted from charts in the neonatal units for infants who were admitted to neonatal care. For stillbirths and infants who died before admission to a neonatal unit, the questionnaires were filled in from obstetric charts. Data from obstetric charts were also used for infants who were admitted to neonatal care in Belgium, Italy, the Netherlands, and Poland. In the regions in France, the Netherlands, and Trent and Northern regions in the United Kingdom, the questionnaires were filled in by external investigators, whereas in Belgium, Denmark, Italy, Poland, and Portugal, the questionnaires were completed by medical personnel in each unit and verified by investigators working for the study. In Belgium, France, Italy, and Poland, the questionnaire was translated using standard procedures. The MOSAIC questionnaire was pretested in all regions to verify its feasibility, and clarifications were made to the instrument. After data collection, the regional teams cross-checked inclusions in the study with birth registers in each maternity unit. Ethics approval was sought for the collection of these data as required in each of the regions.

This analysis of mortality and morbidity uses a subsample of the total cohort that includes live births between 24 and 31 weeks of gestation without lethal congenital anomalies. Infants who are delivered before 24 weeks of gestation are generally considered below the limit of viability in the MOSAIC regions. Furthermore, despite attempts to ensure completeness, some live births at 22 and 23 weeks may not have been included if the birth occurred outside an obstetric ward or if some infants with signs of life were recorded as stillbirths. In the MOSAIC cohort, mortality after live birth was 100% at 22 weeks and 91% at 23 weeks, resulting in 12 infants who survived to discharge.

Infants with lethal congenital anomalies were also excluded from this analysis. Infants were considered to have a lethal congenital anomaly when the principal cause of death was a congenital anomaly or when they had another principal cause of death in association with a lethal congenital anomaly. Only infants who had lethal congenital anomalies and died during hospitalization were considered. Seven deaths that occurred in the labor ward were excluded from the analysis because they were associated with an anomaly detected during the pregnancy but the cause of death was not clearly defined.

The main outcome variables were in-hospital mortal-

TABLE 1 Very Preterm Birth Rates and Characteristics of Very Preterm Live Births in 10 European Regions in 2003

Country	Region	All Live Births in Region, N ^a	Live Births 24–31 wk, n	Very Preterm Birth Rate		GA		Characteristics of Live Births 24–31 wk				
				Rate	95% CI	Mean	SD	%	Mean	SD	%	Maternal Age ≥35 y
Belgium	Flanders	60 118	549	9.1	8.4–9.9	28.6	2.2	13	1195	379	58	13 ^b
Denmark	Eastern region	33 961	323	9.5	8.5–10.5	28.7	2.1	11	1234	395	53	24
France	Ile-de-France	83 935	860	10.2	9.6–10.9	28.7	2.1	10	1185 ^b	371	52	24
Germany	Hesse	51 907	598	11.5	10.6–12.4	28.5	2.2	13	1198	397	55	25
Italy	Lazio	51 743	437	8.4 ^b	7.7–9.2	28.7	2.2	12	1227	399	51	32 ^b
Netherlands	Eastern and Central	47 876	364	7.6 ^b	6.8–8.4	29.1 ^b	1.9	7	1244 ^b	374	53	16
Poland	Wielkopolska/Lubuskie	42 947	376	8.8	7.9–9.7	28.4	2.3	16	1245 ^b	433	52	22
Portugal	Northern	35 207	271	7.7 ^b	6.8–8.6	28.5	2.0	10	1178	369	56	20
United Kingdom	Northern	30 158	394	13.1 ^b	11.8–14.3	28.4	2.2	13	1203	379	57	17
United Kingdom	Trent	56 611	736	13.0 ^b	12.1–13.9	28.7	2.1	10	1206	368	52	15 ^b
All regions		494 463	4908	9.9	9.7–10.2	28.6	2.1	11	1208	385	54	21

The population of very preterm births includes infants who were born alive between 24 and 31 weeks of gestation without lethal congenital anomalies.

^a All live births in the region include births of any GA recorded in the region during the study period.

^b CIs do not overlap with those of the 10-region average.

ity and neurologic and respiratory morbidity. In-hospital mortality included deaths in the labor ward and during hospitalization in a neonatal unit before discharge home from the hospital or into long-term care. Neurologic morbidity was defined as whether the infant had a diagnosis of intraventricular hemorrhage (IVH) grades III and IV using the classifications defined by Papile et al¹⁹ or cystic periventricular leukomalacia (PVL). Respiratory morbidity was BPD, defined as oxygen dependence or ventilation, including nasal continuous positive airway pressure, at 36 weeks of GA. Morbidity rates are presented for the infants who survived to discharge. We also computed the rates of infants who were discharged from hospital with these morbidities with respect to the number of total live births in each region.

Rates in each region are compared with the 10-region average using 95% exact confidence intervals. For simplicity, the 10-region average was not weighted to adjust for the sample sizes within the regions; differences between the weighted and nonweighted averages were slight. Mortality and morbidity rates were standardized for GA and gender using direct standardization, meaning that we applied rates in each GA and gender stratum to the GA and gender distribution within the total cohort. Direct standardization provides the rate that we would expect to find in each region if they all had the same distribution of GA and gender as observed within the total cohort. Analyses were conducted using Stata 8.0 SE (Stata Corp, College Station, TX).

RESULTS

The MOSAIC cohort included 4908 very preterm infants who were born alive between 24 and 31 weeks without lethal congenital anomalies (Table 1). These very preterm live births represented 9.9 per 1000 total live births. Rates of very preterm live birth were similar in many of the regions, with the exception of the 2 English regions, where rates were significantly higher than the 10-region average (13 per 1000), and the Dutch, Italian, and Portuguese regions, where rates were lower (<8.5 per 1000).

Mean GA and birth weight in the cohort were 28.6 weeks and 1208 g, respectively. The Netherlands had a lower proportion of infants born at 24 and 25 weeks and a higher average GA (29.1). In the Polish region, the proportion of infants at 24 and 25 weeks was higher (16% vs 11%), but this difference did not attain statistical significance ($P = .1$). In the Polish and Dutch cohorts, mean birth weights were significantly higher than the 10-region average, by ~35 g; in France, mean birth weights were significantly lower, by 23 g. Differences in the proportion of male infants were not statistically significant, although the proportion ranged from 51% to 58%. There were also differences in maternal age between the regions, with a higher proportion of mothers ≥35 in the Italian region and a lower proportion in Flanders and the Northern region of the United Kingdom.

Table 2 displays in-hospital mortality rates, for which the 10-region average was 14.2%. Crude mortality rates ranged from 7.9% (Hesse in Germany) to 24.7% (Wielkopolska and Lubuskie region in Poland). Both of these rates were statistically different from the 10-region average. After standardization on GA and gender, Hesse and the Northern region in the United Kingdom had significantly lower in-hospital mortality rates than the regional average (7.3% and 9.2%, respectively), and the Netherlands and the Polish regions had significantly higher mortality rates (21.4% and 21.5%, respectively).

Figure 1 presents standardized in-hospital mortality rates for infants 24 to 27 weeks of gestation and those between 28 and 31 weeks of gestation. For infants who were born before 28 weeks of gestation, the 10-region average was 36.3% with mortality rates ranging from lows of 18.3% (Hesse-Germany) and 25.3% (Northern region in the United Kingdom) to 50.8% in the Polish regions and 57.9% in the region from the Netherlands. For infants who were born at ≥28 weeks of gestation, the 10-region average was 5.2%. In low-mortality countries, 3% died before discharge from the hospital, whereas elsewhere, the proportion was ~7%, with a

TABLE 2 In-hospital Mortality of Very Preterm Infants

Country	Region	N	Crude In-hospital Mortality Rate		Standardized In-hospital Mortality Rate ^a	
			Per 100 Live Births	95% CI	Per 100 Live Births	95% CI
Belgium	Flanders	549	16.0	13.1–19.4	15.6	13.3–17.9
Denmark	Eastern	323	10.8	7.7–14.7	11.1	8.1–14.2
France	Ile-de-France	860	14.8	12.5–17.3	15.6	13.4–17.8
Germany	Hesse	598	7.9 ^b	5.8–10.3	7.3 ^b	5.4–9.2
Italy	Lazio	437	17.6	14.2–21.5	17.6	14.5–20.6
Netherlands	Eastern and Central	364	15.7	12.1–19.8	21.4 ^b	18.4–24.4
Poland	Wielkopolska and Lubuskie	376	24.7 ^b	20.5–29.4	21.5 ^b	18.1–24.9
Portugal	Northern	271	15.9	11.7–20.8	16.6	12.7–20.4
United Kingdom	Trent	736	11.8	9.6–14.5	12.2	10.2–14.2
United Kingdom	Northern	394	10.4	7.6–13.2	9.2 ^b	6.7–11.7
All regions		4908	14.2	13.2–15.2	—	—

The population includes infants who were born alive between 24 and 31 weeks of gestation without lethal congenital anomalies. In-hospital mortality includes deaths in the labor ward and deaths that occurred during hospitalization in a neonatal unit. — indicates data not available.

^a Rates are standardized for GA and gender.

^b CIs do not overlap with those of the 10-region average.

high of 9.6% in the Polish region. In general, patterns were the same for both GA groups, with 2 exceptions. In the Netherlands, mortality after 27 weeks was in line with the 10-region average, whereas extremely preterm mortality was higher. In Denmark, mortality was lower for infants after 27 weeks but within the 10-region average for extremely preterm infants.

Figure 2 shows the proportion of survivors to discharge after live birth at 24 to 32 weeks who were born before 28 weeks, subdivided into 2 groups: 24 to 25 weeks and 26 to 27 weeks. Overall, one fifth of all survivors were born before 28 weeks, and most regions had results similar to the 10-regional average. There were several exceptions, however. The region in the Netherlands had a very small proportion of the total cohort <28 weeks and no survivors under 26 weeks, whereas in the Hesse region in Germany and the Northern region in the United Kingdom, a greater proportion of survivors were born before 28 weeks of gestation.

Table 3 presents crude and standardized rates of neurologic and respiratory morbidity for infants who survived to discharge. Rates were calculated excluding infants who had missing data on morbidity; in most regions, these cases represented <1.5% of the total. Rates of missing data were higher in the Danish region (7%) and the Northern region in the United Kingdom (5%). In the Danish region, cranial ultrasound scans were not always conducted when infants were considered at low risk, and infants with missing data had higher mean GA (29.8 vs 28.9; $P < .05$). In the Northern region of the United Kingdom, the mean GA of these infants was similar to other infants.

The combined prevalence of IVH grades III and IV and cystic PVL in the 10 regions was 7.4% for infants who survived to discharge, whereas BPD was present for 15.8% of infants. The regions in France and Denmark had significantly lower rates of neurologic morbidity (<4%), whereas those in Italy and Poland had higher rates (11.8% and 15.7%, respectively). The Lazio region

of Italy had lower rates of BPD, whereas the Northern region in the United Kingdom had higher rates. Standardized morbidity rates were lower than crude rates in low-mortality regions. The standardized rate of neurologic morbidity decreased from 7.6% to 6.8% and respiratory morbidity from 18.8% to 15.7% in Hesse and from 7.7% to 6.7% and 25.2% to 21.8%, respectively, in the Northern region of the United Kingdom.

Table 4 presents the rates of infants discharged from the hospital after very preterm birth with respect to total live births in each region. Rates are presented for all infants 24 to 31 weeks of gestation and those with a diagnosis of IVH/PVL alone as well as a diagnosis of IVH/PVL and/or BPD. Overall, 85.2 infants per 10 000 total births were discharged from the hospital after very preterm birth, with a range from 64.1 to 117.1 between regions. Infants who were discharged with IVH/PVL represented 6.2 per 10 000 births, on average, with a range from 2.1 to 10.2. Infants with IVH/PVL and/or BPD represented 17.2 per 10 000 with a low of 10.0 and a high of 31.2.

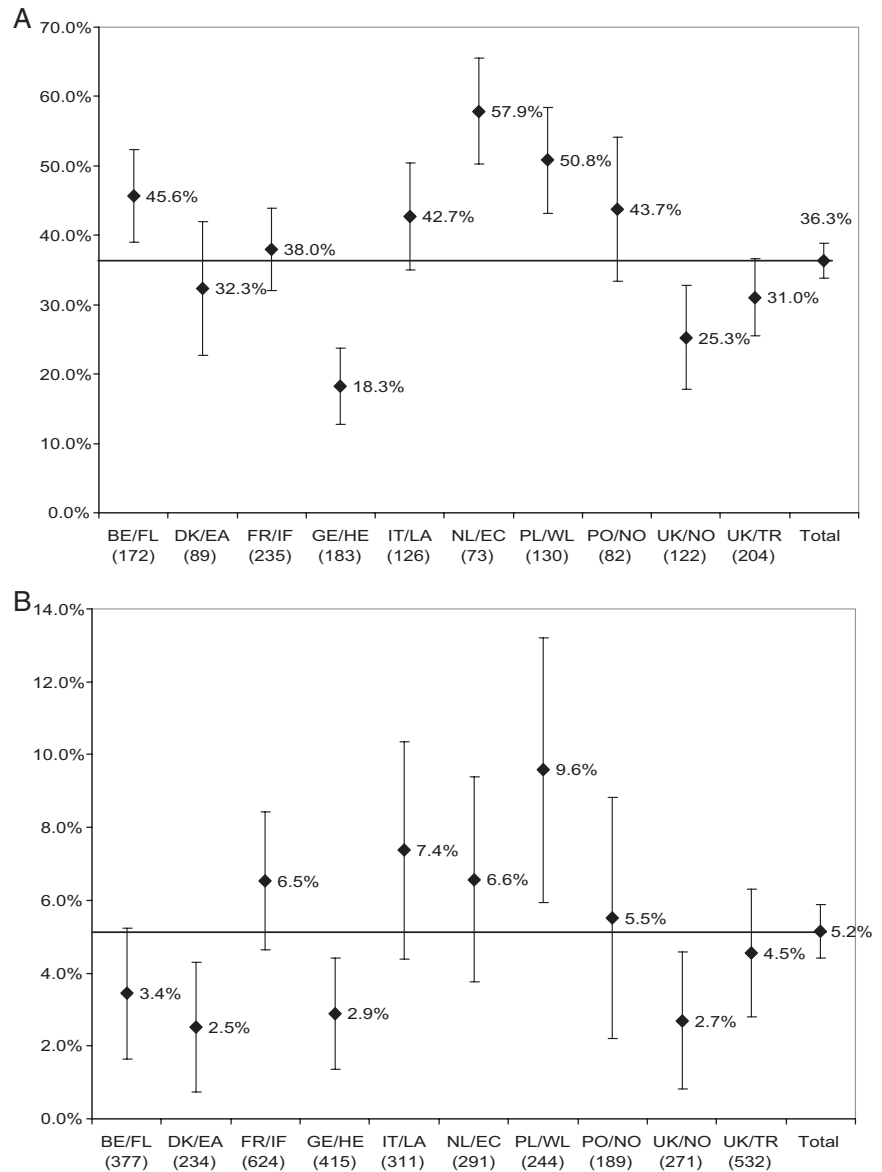
DISCUSSION

We found marked differences in very preterm birth rates as well as mortality and short-term morbidity in 10 population-based cohorts of very preterm infants from regions that participated in the MOSAIC study. In the total cohort, 14.2% of infants who were born alive between 22 and 31 weeks of gestation died before discharge from the hospital, but standardized mortality was doubled in high- versus low-mortality regions (18%–20% vs 7%–9%). Morbidity among survivors also varied significantly; the combined prevalence of IVH grades III and IV and cystic PVL ranged from 2.6% to >10% and BPD from 10.5% to 21.5%.

Underascertainment was unlikely to be responsible for these regional variations. A standardized approach to data validation was conducted for all regions; inclusions in the MOSAIC cohort were cross-checked with birth

FIGURE 1

Standardized in-hospital mortality rates of very preterm infants according to GA group: A, 24 to 27 weeks' gestation; B, 28 to 31 weeks' gestation. Note that the sample sizes are indicated in parentheses under the region label. The population includes infants who were born alive between 24 and 31 weeks of gestation without lethal congenital anomalies. In-hospital mortality rates include deaths in the labor ward and deaths that occurred during hospitalization in a neonatal unit. Rates were standardized for GA and gender. BE/FL indicates Belgium/Flanders; DK/EA, Denmark/Eastern Region; FR/IF, France/Ile-de-France; GE/HE, Germany/Hess; IT/LA, Italy/Lasio; NL/EC, The Netherlands/Eastern and Central; PL/WL, Poland/Wielkopolska-Lubuskie; PO/NO, Portugal/Northern Region; UK/NO, United Kingdom/Northern Region; UK/TR, United Kingdom/Trent.



registers to ensure completeness, and the study included the full cohort of late fetal losses and live and still births from 22 weeks of GA, making underreporting for live births at 24 weeks less likely. Furthermore, variability in mortality was observed at later GAs, when underreporting was improbable.

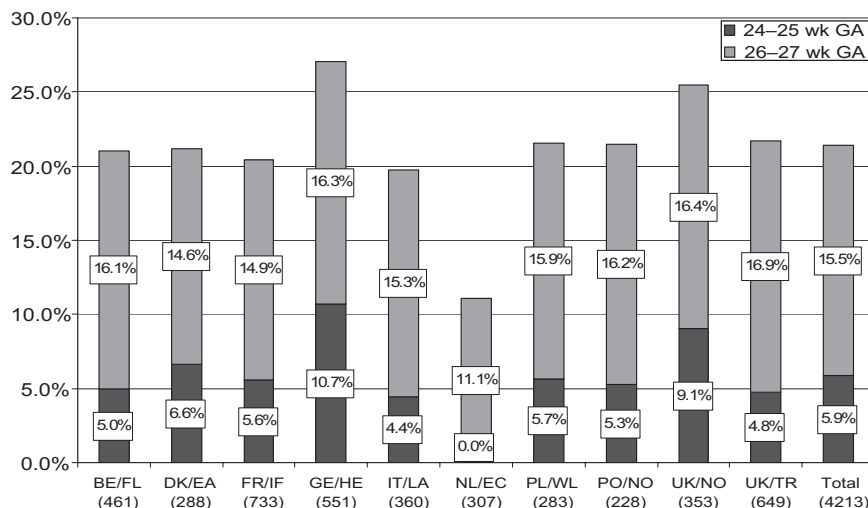
Some of the variability in morbidity could result from different diagnostic practices. For instance, we cannot rule out observer bias in the interpretation of cranial ultrasounds. Oxygen saturation limits may also differ between individual units, affecting decisions related to the use of oxygen and measures of respiratory morbidity^{20,21}; however, the definitions for our indicators of morbidity were established and tested for feasibility before data collection. The diagnosis of IVH grades III and IV was based on cranial ultrasound reporting on the basis of Papile gradings, which are used in all of the regions,¹⁹ and infants who had missing cranial ultrasounds were classified as having missing data for this

indicator. Missing data were <1.5% for most regions. Another source of differential reporting may be varying lengths of stay between regions. Infants were followed until discharge home from the hospital, and it is possible that if some regions have shorter average lengths of stays, then this could affect ascertainment of our end points occurring after discharge from the hospital; however, we believe this bias to be small because our outcomes (death, severe cranial lesions, and oxygen dependence or ventilation at 36 weeks) occur primarily in-hospital.

Mortality and morbidity data have not previously been compared across population-based samples of very preterm infants in Europe. Our principal aim was to assess current rates of mortality and morbidity and their variations between regions using comparable indicators. The only factors for which we adjusted were GA and gender. Although mean GA did not differ significantly in most of the regions, nonsignificant variations in the GA

FIGURE 2

Proportion of live-born very preterm infants who survived to discharge with a GA of <28 weeks. Note that the total number of survivors in each regional cohort is indicated in parentheses under the region label. See the Fig 1 legend for abbreviation definitions.



distribution had an impact on mortality because of the very high mortality at lower gestations. Standardizing on GA and gender did not explain regional differences but tended to accentuate them. In the 2 low-mortality regions, Hesse and the Northern region of the United Kingdom, standardizing for the GA distribution lowered mortality rates. This result suggests that these lower mortality regions may be more active with respect to medically decided preterm deliveries, leading to a greater proportion of extremely preterm live births. Proactive treatment of very preterm infants has been associated

with increased preterm birth rates and lower mortality.²² In contrast, in the Netherlands, standardization had the opposite effect of increasing mortality rates, reflecting the lower proportion of live-born infants in the Netherlands at 24 and 25 weeks, when mortality rates are high. The low proportion of live-born infants at early gestations could reflect policies not to intervene, which may result in a greater number of stillbirths. An analysis of stillbirths in the MOSAIC cohort is in preparation to explore this association.

This study found large differences between regions in

TABLE 3 Crude and Standardized Rates of Neurologic and Respiratory Morbidity, Per 100 Very Preterm Infants Who Survived to Discharge

Country	Region	Total Infants	No. With Missing Data	No. With Diagnosis	Crude Rate Per 100	Standardized Rate ^a	
						Per 100	95% CI
IVH III/IV or cystic PVL							
Belgium	Flanders	461	0	43	9.3	10.0	7.7-12.4
Denmark	Eastern	288	21	7	2.6 ^b	2.6 ^b	0.7-4.5
France	Ile-de-France	733	7	28	3.9 ^b	3.8 ^b	2.4-5.1
Germany	Hesse	551	1	42	7.6	6.8	4.8-6.8
Italy	Lazio	360	4	42	11.8 ^b	12.5 ^b	9.0-16.0
Netherlands	Eastern and Central	307	0	18	5.9	6.1	3.5-8.8
Poland	Wielkopolska and Lubuskie	283	3	44	15.7 ^b	16.7 ^b	12.3-21.2
Portugal	Northern	228	1	18	7.9	8.1	4.6-11.5
United Kingdom	Northern	353	15	26	7.7	6.7	4.1-9.3
United Kingdom	Trent	649	6	39	6.1	6.2	4.4-8.1
All regions		4213	58	307	7.4	—	6.6-8.2
BPD							
Belgium	Flanders	461	0	65	14.1	14.6	11.7-17.5
Denmark	Eastern	288	16	28	10.3 ^b	11.4 ^b	8.1-14.6
France	Ile-de-France	733	17	100	14.0	13.8	11.4-16.2
Germany	Hesse	551	19	100	18.8	15.7	13.0-18.4
Italy	Lazio	360	2	34	9.5 ^b	10.5 ^b	7.6-13.4
Netherlands	Eastern and Central	307	1	34	11.1	11.9	8.4-15.4
Poland	Wielkopolska and Lubuskie	283	34	39	15.7	15.5	11.2-19.8
Portugal	Northern	228	12	26	12.0	12.8	9.0-16.5
United Kingdom	Northern	353	31	81	25.2 ^b	21.8 ^b	17.9-25.7
United Kingdom	Trent	649	2	137	21.2 ^b	21.0 ^b	18.3-23.7
All regions		4213	134	644	15.8	—	14.7-16.9

— indicates rates standardized on regional distribution of age and gender.

^a Rates are standardized for GA and gender.

^b CIs do not overlap with those of the 10-region average.

TABLE 4 Survivors After Very Preterm Birth Per 10 000 Total Live Births, All Infants and Infants With Severe Neurologic and Respiratory Morbidity at Discharge

Country	Region	Live Births in 2003, N ^a	Survivors After Birth Between 24 and 31 wk of Gestation						
			All Infants			Diagnosis of IVH/PVL		Diagnosis of IVH/PVL or BPD	
			<i>n</i>	Rate	95% CI	Rate	95% CI	Rate	95% CI
Belgium	Flanders	60 118	461	76.7	69.7–83.7	7.2	5.0–9.3	16.0	12.8–19.2
Denmark	Eastern	33 961	288	84.8	75.1–94.6	2.1 ^b	0.5–3.6	10.3 ^b	6.9–13.7
France	Ile-de-France	83 935	733	87.3	81.0–93.6	3.3 ^b	2.1–4.6	15.0	12.4–17.6
Germany	Hesse	51 907	551	106.2 ^b	97.3–115.0	8.1	5.6–10.5	24.7 ^b	20.4–28.9
Italy	Lazio	51 743	360	69.6 ^b	62.4–76.7	8.1	5.7–10.6	13.1	10.0–16.3
Netherlands	Eastern and Central	47 876	307	64.1 ^b	57.0–71.3	3.8 ^b	2.0–5.5	10.0 ^b	7.2–12.9
Poland	Wielkopolska and Lubuskie	42 947	283	65.9 ^b	58.2–73.5	10.2 ^b	7.2–13.3	14.9	11.3–18.6
Portugal	Northern	35 207	228	64.8 ^b	56.4–73.1	5.1	2.8–7.6	11.4 ^b	7.8–14.9
United Kingdom	Northern	30 158	353	117.1 ^b	104.9–129.2	8.6	5.3–11.9	31.2 ^b	24.9–37.5
United Kingdom	Trent	56 611	649	114.6 ^b	105.9–123.4	6.9	4.7–9.1	28.8 ^b	24.4–33.2
All regions		494 463	4213	85.2	82.6–87.8	6.2	5.5–6.9	17.2	16.0–18.3

The population of very preterm births includes infants who were born alive between 24 and 31 weeks of gestation without lethal congenital anomalies. — indicates data not available.

^a Live births in the region include births of any GA recorded in the region during the study period.

^b CIs do not overlap with those of the 10-region average.

rates of IVH grades III and IV and PVL as well as BPD among survivors. Data from other population studies have found values within the ranges reported here: between 7% and 10% for neurologic morbidity and 10% and 20% for respiratory morbidity.^{12,23} Some of the differences in crude morbidity rates between regions were explained by increased survival of more immature infants. Adjusting for the GA distribution slightly lowered morbidity rates in low-mortality regions; however, several regions with similar levels of mortality had markedly different rates of morbidity. This result underscores the importance of including data on morbidity in addition to mortality when evaluating the quality of care provision for very preterm infants.

Differences in ethical decision-making in delivery wards and neonatal units provide one explanation for these variations in outcome.²⁴ In the Netherlands, the very high mortality under 28 weeks of gestation reflects a consensus not to intervene actively for extremely preterm infants²⁵; the consensus on nonintervention was illustrated by the low proportion of infants who were born at <28 weeks and survived to discharge. In this region in 2003, no survivors were born before 26 weeks. This extreme result represents, in part, annual variability, because there were survivors who were born before 26 weeks in this region in other years and also in other regions of the Netherlands in 2003.²⁶ Mortality in the Dutch region was in line with the regional average at 28 to 31 weeks of gestation. Ethical decision-making in the neonatal units could also contribute to differences in rates of morbidity when decisions to withhold or to withdraw treatment are made with respect to the presence of severe brain hemorrhaging or other criteria related to short-term morbidity.^{27,28}

Another explanation may be the role of comorbidities and, in particular, congenital anomalies. We excluded lethal congenital anomalies from this analysis because there are wide differences in screening and termination practices between regions that could affect the propor-

tion of deaths associated with a congenital anomaly,²⁹ a topic on which the MOSAIC group has reported elsewhere; however, the presence of nonlethal congenital anomalies also increases the probability of death.³⁰ This risk factor may be particularly prevalent in Poland, where terminations of pregnancy for congenital anomalies are highly restricted.

Decisions for infants at the limit of viability were unlikely to be the sole explanation for the variability across regions, because disparities persisted for infants who were older than 27 weeks of gestation, when a consensus on intervention is widespread. Congenital anomalies, of potential importance in some regions, nonetheless contribute to a small proportion of mortality and morbidity among very preterm infants without lethal anomalies. These results thus raise essential questions about other causes for regional variations in outcome. The organization of perinatal care for very preterm infants such as the place of delivery and the characteristics of the units where they are hospitalized have been shown in many studies to have an impact on mortality and morbidity.^{31–35} Medical practices, such as those related to artificial ventilation and oxygen use, for instance, may also affect morbidity.²⁰ Finally, variability in the prevalence of certain complications of pregnancy could also be a contributing factor; risks for short-term morbidity have been related to prenatal infections and hypertension.^{36,37} Differences in the distribution of maternal age between the regions, for instance, could contribute to a higher prevalence of complications, such as hypertension.

Our results also raise questions about the long-term impact of differences in preterm birth rates, in-hospital mortality, and short-term morbidity. For instance, if ~8% of infants who are <32 weeks are estimated to develop cerebral palsy (estimates from 5%–10% in the literature^{1–4}), then the range in population incidence of survivors in the MOSAIC regions per 10 000 births (64.1–117.1) would correspond to a low of 5 and a high of 9 expected cases of cerebral palsy per 10 000 live

births. This difference is substantial when related to observed cerebral palsy rates of ~20 per 10 000 live births.^{2,4,38} The regions also differed by the proportion of survivors with a GA of <28 weeks, a key factor associated with higher rates of childhood disabilities^{1,2,5,39} as well as the prevalence of IVH-PVL and BPD, which are the principal neonatal morbidities associated with a higher risk for impairment in childhood.^{40–45} Comparative follow-up studies are needed to provide this information and make it possible to evaluate the health impacts of differences in treatment and outcome in the perinatal period.

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Differences in Rates and Short-term Outcome of Live Births Before 32 Weeks of Gestation in Europe in 2003: Results From the MOSAIC Cohort

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