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H. Ehrhardt, Thomas Desplanches, A. F. J. van Heijst, L. Toome, A. Fenton, Héloise Torchin, Alexandra Nuytten, J. Mazela, Jennifer Zeitlin, R. F. Maier

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Mode of Delivery and Incidence of Bronchopulmonary Dysplasia: Results from the Population-Based EPICE Cohort

Harald Ehrhardt[a] Thomas Desplanches[b, c] Arno F.J. van Heijst[d] Liis Toome[e, f] Alan Fenton[g] Héloïse Torchin[b, h] Alexandra Nuytten[i, j] Jan Mazela[k] Jennifer Zeitlin[b] Rolf F. Maier[l] on behalf of the EPICE/SHIPS Research Group

[a]Department of General Pediatrics and Neonatology, Universities of Giessen and Marburg Lung Center (UGMLC), Member of the German Center for Lung Research (DZL), Justus-Liebig-University Giessen, Giessen, Germany; [b]Obstetrical, Perinatal, and Pediatric Epidemiology Team, Center of Research in Epidemiology and Statistics (U1153), INSERM, Université de Paris, Paris, France; [c]Department of Gynaecology, Obstetrics, Foetal Medicine and Infertility, Dijon University Hospital, Dijon, France; [d]Department of Neonatology, Radboud University Medical Center, Nijmegen, The Netherlands; [e]Department of Neonatal and Infant Medicine, Tallinn Children's Hospital, Estonia University, Tallinn, Estonia; [f]Department of Pediatrics, University of Tartu, Tartu, Estonia; [g]Newcastle Neonatal Service, Newcastle University, Newcastle upon Tyne, UK; [h]Department of Neonatal Pediatrics, Cochin Port Royal Hospital, APHP, Paris, France; [i]Department of Neonatology, Jeanne de Flandre Hospital, CHU Lille, University of Lille, Lille, France; [j]ULR 2694 – METRICS: Évaluation des Technologies de Santé et des Pratiques Médicales, CHU Lille, University of Lille, Lille, France; [k]Department of Neonatology, Poznan University of Medical Sciences, Poznan, Poland; [l]Children's Hospital, University Hospital, Philipps University Marburg, Marburg, Germany

Keywords
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Abstract
Introduction: Bronchopulmonary dysplasia (BPD) represents a tremendous disease burden following preterm birth. The strong association between compromised gas exchange after birth and BPD demands particular focus on the perinatal period. The mode of delivery can impact on lung fluid clearance and microbial colonization, but its impact on BPD and potential trade-off effects between death and BPD are not established. ***Methods:*** A total of 7,435 live births (24+0 to 31+6 weeks postmenstrual age) in 19 regions of 11 European countries were included. Principal outcomes were death and BPD at 36 weeks. We estimated unadjusted and adjusted associations with mode of delivery using multilevel logistic regression to account for clustering within units and regions. Sensitivity analyses examined effects, taking into consideration regional variations in C-section rates. ***Results:*** Compared to vaginal delivery, delivery by C-section was not associated with the incidence of BPD (OR 0.92, 95% CI: 0.68–1.25) or the composite outcome of death or BPD (OR 0.94, 95% CI: 0.74–1.19) after adjustment for perinatal and neonatal risk factors in the total cohort and in pregnancies for whom a vaginal delivery could be considered. Sensitivity analyses among singletons, infants in cephalic presentation, and infants of ≥26+0 weeks of gestation did not alter the results for BPD, severe BPD, and death or BPD, even in regions

Karger@karger.com
www.karger.com/neo

Correspondence to:
Harald Ehrhardt, harald.ehrhardt@paediat.med.uni-giessen.de

with a high C-section rate. ***Conclusions:*** In our population-based cohort study, the mode of delivery was not associated with the incidence of BPD. The intention to reduce BPD does not justify a C-section in pregnancies where a vaginal delivery can be considered.

Introduction

Large differences in prevalence of bronchopulmonary dysplasia (BPD) exist between and within countries which cannot be explained solely by heterogeneity in genetic background, behavioral and social factors, attitudes about the provision of active care, and differences in respiratory management [1]. BPD leads to lifelong restrictions in lung function, excess use of healthcare services, socioeconomic costs and poses a high risk for abnormal somatic growth and psychomotor development. The origins of BPD are multifactorial and include infection, mechanical ventilation (MV), and oxygen toxicity [2]. Despite all the advances in care, the disease burden of BPD has remained unchanged over past decades [3].

Efficient lung fluid clearance after birth is one important mechanism for establishing postnatal gas exchange [4]. Respiratory instability after birth in the term neonate born by caesarian section (C-section) before the onset of labor has been attributed to an inadequate fetal stress response due to the absence of uterine contractions before birth and inefficient lung fluid clearance. In preterm infants, inefficient lung fluid clearance in addition to immaturity of the lung and surfactant deficiency is acknowledged to contribute to respiratory distress after birth. Lung water content in the immature lung is higher than at term [5]. The decreased lung fluid clearance after birth is attributed to immaturity per se and is associated with prolonged need for MV and oxygen supply in preterm infants [6]. Respiratory symptoms can persist for several days despite the beneficial effects of postnatal positive airway pressure on surfactant release and lung fluid clearance and are highly interrelated to the development of BPD [6, 7].

The Cochrane meta-analysis on this topic did not detect any advantage for the preterm for one of the two delivery modes, but its validity is limited by the paucity of randomized controlled trials [8]. One systematic review including 14 nonrandomized studies detected a reduced risk of death in singleton infants of <28 weeks gestation in a vertex position delivered by C-section [9]. However, these results require cautious interpretation because of indication biases in the absence of randomization. No conclusive data as to the best mode of delivery exist for the important morbidities of preterm infants including intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, and BPD. When separately considering breech presentation, a significant reduction of mortality and severe intraventricular hemorrhage was observed with C-section in the latest meta-analysis with the highest benefits for the smallest infants [10]. However, there is not enough scientific proof to underpin evidence-based recommendations, and current decision-making is mainly guided by medical experience and obstetric indication.

Few of these studies have investigated BPD as an outcome, and there is a lack of evidence as to how mode of delivery impacts on incidence. The objective of this study was to evaluate the impact of the mode of delivery on the incidence of BPD and to identify potential trade-offs between mortality and BPD in a large population-based cohort of preterm infants. Our hypothesis was that because of improved postnatal lung fluid clearance as well as colonization with the own mother's microbiome in infants delivered vaginally, the pulmonary outcome of preterm infants would be better after vaginal delivery compared to C-section and lead to reduced BPD risk.

Methods

Study Design

The "Effective Perinatal Intensive Care in Europe" (EPICE) cohort is a prospective population-based study cohort that enrolled all preterm infants born from 22+0 to 31+6 weeks' gestational age (GA) in 19 geographically and organizationally diverse regions in 11 European countries over varying 12-month periods from April 2011 to June 2012 with the exception of a French region where data collection occurred over 6 months. Further cohort details have been described elsewhere [11]. Data were collected from patient records in obstetric and neonatal departments using a standardized questionnaire with pretested definitions. Infants were followed up until death or discharge home.

Study Population

We limited our main analysis sample to the population of infants for whom a vaginal delivery might be considered as it was not possible to obtain a comparable group of infants delivered vaginally for indications where delivery is always or nearly always by C-section. Therefore, we excluded C-sections for maternal and fetal indications; preterm births associated with preeclampsia/eclampsia/hemolysis, elevated liver enzymes, and low platelet count; or suspected fetal growth restriction or other complications, as previously done for analyses within the EPICE cohort [12]. We also excluded infants who were delivered <24+0 weeks

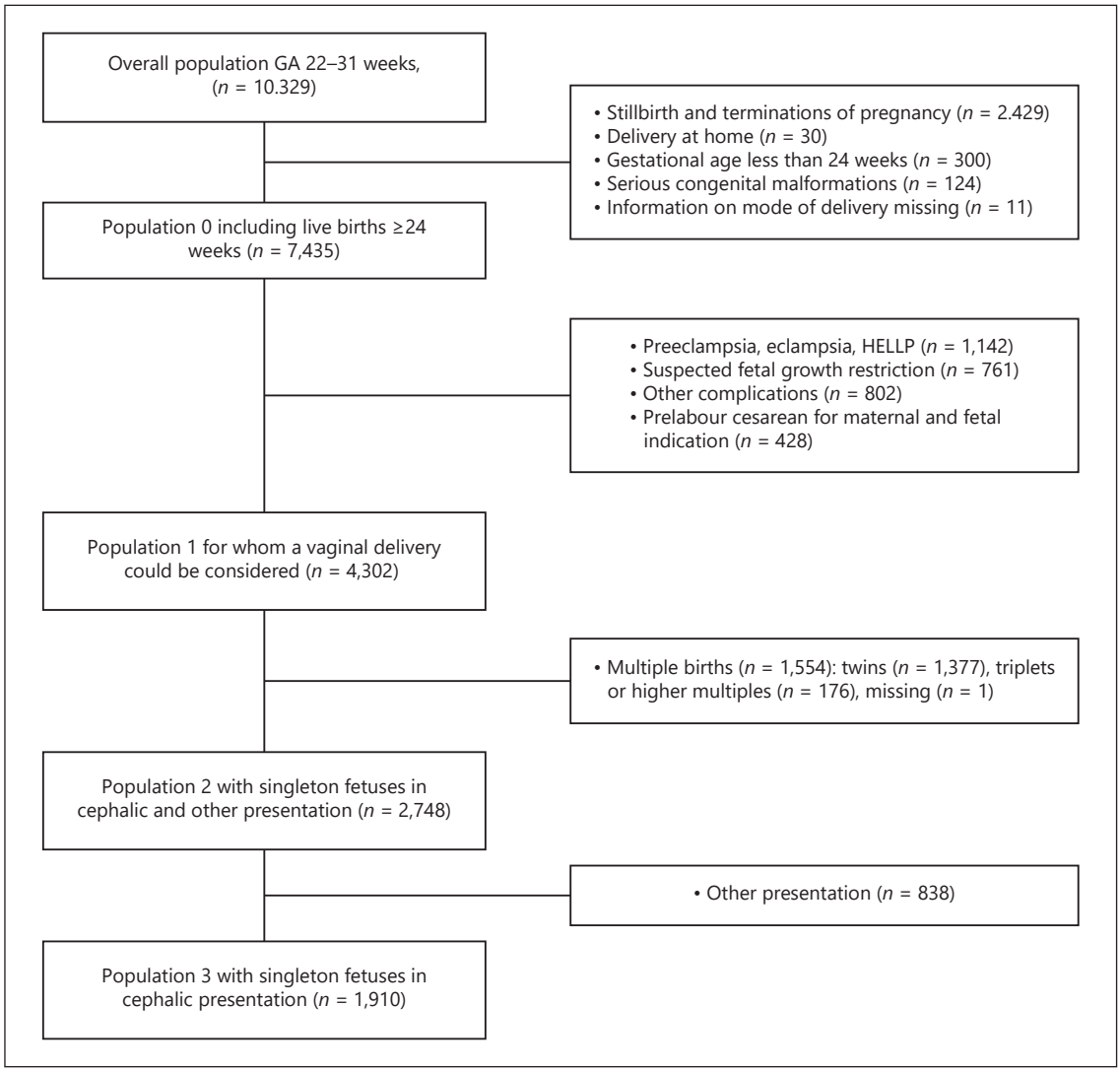

Fig. 1. Flowchart of inclusion and exclusion of infants into the study population and subpopulations. PPROM, preterm premature rupture of membranes; HELLP, hemolysis, elevated liver enzymes, and low platelet count.

gestation because of heterogeneous management in this subgroup between regions, infants with serious congenital malformations, infants delivered at home, and when information on the mode of delivery was missing. Furthermore, infants from the three UK regions were excluded from the separate analysis of severe BPD as data on FiO_2 requirements at 36 weeks were not recorded.

We also carried out analyses in the total population without exclusions to assess the impact of our population selection criteria on the results as well as in more restricted population subgroups: infants of ≥26+0 weeks gestation, to account for differences in attitudes toward delivery by C-section at younger GA between centers and regions, singleton pregnancies, and singletons in cephalic presentation in order to exclude potential disparities in risk associated with multiple births and breech presentations (Fig. 1).

Definition of Outcomes and Covariates

Our primary outcome was moderate/severe BPD that was based on the NICHD consensus definition: infants were categorized as moderate BPD if they required <30% oxygen and as severe BPD with ≥30% oxygen and/or need for positive pressure support at 36 weeks' GA [13]. Patients were classified to suffer from mild BPD with oxygen dependency for at least 28 days of life but not fulfilling any BPD criterion at 36 weeks. Mild BPD cases were grouped with infants without BPD. A secondary outcome was moderate or severe BPD and/or in-hospital mortality in all infants given active treatment. Our exposure was C-section. Maternal characteristics included in the analyses were maternal age and parity. GA was defined as the best obstetric assessment, based on information on the last menstrual period and routine ultrasound measure. Small for GA (SGA) was birth weight (BW) <10th percentile of intrauterine references developed for the cohort [14].

Table 1. Mode of delivery and maternal and neonatal characteristics in population 1

Characteristics, *n* (%)	Mode of delivery		*p* value	Missing data, %
	C-section (*N* = 2,103)	vaginal delivery (*N* = 2,199)		
Maternal age				
<35 years	1,515 (72.0)	1,771 (80.5)	0.0001	<1
≥35 years	582 (27.7)	419 (19.0)		
Nulliparous mother	1,167 (55.5)	1,207 (54.8)	0.92	1.2
Previous caesarean section*	277/834 (33.3)	153/900 (17.0)	0.01	4
Multiple pregnancies	1,024 (48.7)	529 (24.0)	0.001	0
Antepartum maternal hemorrhage after 20 weeks GA	328 (15.6)	472 (21.4)	0.005	3.2
Admission for preterm labor/contractions after 20 weeks GA	1,240 (58.9)	1,556 (70.7)	0.001	2.9
PPROM (>12 h)	649 (30.8)	737 (33.5)	0.04	2.5
Any antenatal steroids	1,888 (89.7)	1,845 (83.9)	0.001	<1
GA, weeks				
24–25	167 (7.9)	451 (20.5)	0.001	0
26–27	399 (19.0)	415 (18.9)		
28–29	581 (27.6)	446 (20.3)		
30–31	956 (45.5)	887 (40.3)		
Sex (female)	926 (44.0)	934 (42.5)	0.30	0
Cephalic presentation	1,009 (47.9)	1,770 (80.5)	0.001	4
BW				
<3rd percentile	215 (10.2)	72 (3.3)	0.001	<1
3rd to 10th percentile	240 (11.4)	163 (7.4)		
>10th percentile	1,648 (78.4)	1,963 (89.3)		
Apgar score <7 at 5 min	357 (17.0)	392 (17.8)	0.46	0
Doses of surfactant				
0	892 (43.8)	926 (43.9)	0.24	3.6
1	799 (39.3)	790 (37.5)		
2	343 (16.9)	394 (18.7)		
CPAP				
Total number of treated infants	1,716 (82.5)	1,693 (78.6)	0.002	1.6
Duration of CPAP, days	6 [2–19.5]	7 [2–28]	0.03	4.0
MV				
Total number of treated infants	1,223 (58.8)	1,272 (59.8)	0.49	2.3
Duration of MV, days	3 [2–9]	4 [2–15]	0.03	15.5
Supplemental oxygen				
Total number of treated infants	1,376 (77.8)	1,205 (70.1)	0.001	19.4[a]
Duration of oxygen, days	4 [1–24]	3 [0–31]	0.29	2.4[b]
Postnatal steroids for other reasons	111 (5.3)	136 (6.4)	0.03	7.4
Systematic postnatal steroids for BPD	139 (6.6)	196 (9.2)	0.003	6.0
PDA NSAID therapy	341 (16.3)	392 (18.3)	0.003	4.9
Any maternal breast milk at discharge	1,120 (60.5)	1,089 (57.8)	0.10	2.1

Data are presented as *n* and proportions (%) in brackets or median and IQR in brackets. χ^2 and Wilcoxon tests were applied to test for statistical analyses. C-section, cesarean section; PPROM, preterm premature rupture of membranes; SGA, small for gestational age; CPAP, continuous positive airway pressure; MV, mechanical ventilation; BPD, bronchopulmonary dysplasia; PDA, persistent ductus arteriosus; NSAID, nonsteroidal anti-inflammatory drugs; GA, gestational age; BW, birth weight; IQR, interquartile range. [a] Data on FiO_2 requirements not available for infants from the three UK regions, [b] infants discharged on home supplemental oxygen were excluded as total duration is not available. * Calculated in multiparous.

Antenatal steroid administration was counted when at least one dose was given before delivery irrespective of the time interval to delivery. Preterm premature rupture of membranes (PPROM) was defined as >12 h before the onset of labor.

Statistical Analysis

Baseline characteristics were compared by mode of delivery using χ^2 tests for proportions and Wilcoxon tests for medians. The association between mode of delivery and BPD and death or

Table 2. Outcomes of BPD and death or BPD in very preterm infants by the mode of delivery

Outcomes	*N*	C-section, *n*/*N* (%)	Vaginal delivery (reference), *n*/*N* (%)	Model 0, mixed effects, crude OR [95% CI]	Model 1, mixed effects, adjusted OR [95% CI][a]
Population 0					
Death/BPD	7,435	1,032/4,928 (20.9)	654/2,359 (27.7)	0.71 [0.62–0.82]	0.82 [0.64–1.05]
Death	7,435	456/5,020 (9.0)	326/2,415 (13.5)	0.62 [0.53–0.74]	0.92 [0.71–1.19]
Moderate/severe BPD	6,505	576/4,472 (12.9)	328/2,033 (16.1)	0.85 [0.72–1.01]	0.77 [0.57–1.05]
Population 1					
Death/BPD	**4,302**	**388/2,063 (18.9)**	**583/2,147 (27.1)**	**0.64 [0.54–0.76]**	**0.81 [0.61–1.09]**
Death	**4,302**	**187/2,103 (8.9)**	**288/2,199 (13.1)**	**0.63 [0.51–0.77]**	**0.89 [0.65–1.22]**
Moderate/severe BPD	**3,826**	**201/1,876 (10.7)**	**295/1,859 (15.9)**	**0.70 [0.56–0.88]**	**0.77 [0.53–1.12]**
Population 2					
Death/BPD	2,748	220/1,061 (20.7)	450/1,638 (27.5)	0.71 [0.57–0.88]	0.85 [0.59–1.21]
Death	2,748	110/1,079 (10.2)	210/1,669 (12.6)	0.75 [0.56–0.97]	0.95 [0.64–1.40]
Moderate/severe BPD	2,427	110/951 (11.6)	240/1,428 (16.8)	0.69 [0.52–0.93]	0.72 [0.45–1.16]
Population 3					
Death/BPD	1,910	88/504 (17.5)	317/1,380 (23.0)	0.72 [0.53–0.96]	1.21 [0.79–1.86]
Death	1,910	44/509 (8.6)	135/1,401 (9.6)	0.82 [0.56–1.20]	1.44 [0.86–2.42]
Moderate/severe BPD	1,730	44/460 (9.6)	182/1,245 (14.6)	0.64 [0.43–0.96]	0.94 [0.54–1.65]

Results from a generalized linear mixed model with multilevel logistic regressions with regions and centers and adjusted for maternal age, previous C-section, multiple pregnancy, antepartum maternal hemorrhage after 20 weeks GA, admission for preterm labor/contractions after 20 weeks, antenatal steroids, PPROM, gestational age, SGA, sex, and presentation. Results for population 1 (main analysis sample of infants for whom a vaginal delivery might be considered) are printed in bold. C-section, cesarean section; BPD, bronchopulmonary dysplasia. [a]Multiple pregnancy has not been used as an adjustment factor in models for population 2 and population 3. In addition, presentation has not been used as an adjustment factor in models for population 3. Population 0: all live births ≥24 weeks without deliveries at home, serious congenital malformations, and with information on the mode of delivery. Population 1: population for whom a vaginal delivery could be considered. Population 2: singleton fetuses in cephalic and other presentation. Population 3: singleton fetuses in cephalic presentation.

BPD was investigated applying hierarchical mixed models with the unit and country as random effects to take into consideration treatment variations in C-section rates, in respiratory management, and oxygen saturation targeting and the hierarchical structure of our data [12, 15]. As prenatal risk factors relevant for the outcomes were not equally distributed between the vaginal delivery and C-section groups, the following variables were considered as potential baseline confounders: GA, SGA, sex, antenatal steroids, PPROM, maternal age, previous C-section, multiple pregnancy, antepartum maternal hemorrhage after 20 weeks GA, admission for preterm labor/contractions after 20 weeks, and presentation. Systemic postnatal corticosteroid administration to treat BPD, treatment of persistent ductus arteriosus (PDA) with nonsteroidal anti-inflammatory drugs (NSAIDs), and provision of maternal milk at discharge were assumed to be postnatal treatment confounders. We conducted additional sensitivity analyses to test for differences between regions with higher (>50%; Denmark, Portugal, Poland, Sweden, Italy, Germany) and lower (<50%; The Netherlands, Estonia, UK, France, Belgium) C-section rates. This analysis takes into account the reduced indication bias in countries with high C-section rates to study a biological explanation for the association between C-section and BPD. All analyses were done with SAS software version 9.4.

Results

Cohort Characteristics and Variable Distribution by the Mode of Delivery

Of 7,435 infants born between 24+0 and 31+6 weeks' GA (= population 0), 4,302 were included in our main analysis sample (= population 1) (Fig. 1). In this analysis sample of births for which a vaginal delivery might be considered, 51.1% were vaginal deliveries (Table 1). Births in the C-section group were more likely to have mothers ≥35 years, with a previous C-section, to have received antenatal steroids and to have higher GA, be from a multiple pair, SGA, and in a breech presentation, while the likelihood of antepartum hemorrhage, admission for preterm labor/contractions, and PPROM was reduced (Table 1; online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000524337). The overall mortality rate was 11.0%, and the BPD rate was 13.0% (Table 2). BPD was more frequently observed in infants with antepartum maternal hemorrhage, admission for preterm labor/contractions, singleton pregnan-

Table 3. Sensitivity analysis in the subgroup of preterm infants of ≥26+0 weeks of gestation

Outcomes	*N*	C-section, *n*/*N* (%)	Vaginal delivery (reference), *n*/*N* (%)	Model 0, mixed effects, crude OR [95% CI]	Model 1, mixed effects, adjusted OR [95% CI][a]
Population 0					
Death/BPD	6,584	797/4,582 (17.4)	303/1,867 (16.2)	1.14 [0.96–1.34]	0.80 [0.62–1.04]
Death	6,584	318/4,672 (6.8)	125/1,912 (6.5)	1.00 [0.80–1.25]	0.99 [0.73–1.35]
Moderate/severe BPD	6,139	479/4,264 (11.2)	178/1,742 (10.2)	1.23 [1.00–1.52]	0.70 [0.50–0.97]
Population 1					
Death/BPD	**3,684**	**282/1,898 (14.8)**	**265/1,705 (15.5)**	**0.98 [0.79–1.21]**	**0.82 [0.60–1.11]**
Death	**3,684**	**123/1,936 (6.3)**	**112/1,748 (6.4)**	**0.92 [0.70–1.21]**	**1.00 [0.68–1.46]**
Moderate/severe BPD	**3,448**	**159/1,775 (8.9)**	**153/1,593 (9.6)**	**1.02 [0.78–1.34]**	**0.73 [0.49–1.09]**
Population 2					
Death/BPD	2,321	166/972 (17.1)	206/1,307 (15.8)	1.12 [0.86–1.44]	0.91 [0.63–1.31]
Death	2,321	86/989 (8.7)	86/1,332 (6.5)	1.25 [0.91–1.73]	1.22 [0.78–1.91]
Moderate/severe BPD	2,148	80/886 (9.0)	120/1,221 (9.8)	0.95 [0.67–1.35]	0.72 [0.43–1.20]
Population 3					
Death/BPD	1,661	75/482 (15.6)	161/1,158 (13.9)	1.15 [0.83–1.61]	1.24 [0.80–1.91]
Death	1,661	38/486 (7.8)	61/1,175 (5.2)	1.37 [0.88–2.13]	1.81 [1.03–3.16]
Moderate/severe BPD	1,561	37/444 (8.3)	100/1,097 (9.2)	0.96 [0.61–1.50]	0.91 [0.51–1.64]

Analyses from Table 2 were restricted to preterm infants with a GA of ≥26+0 weeks. Results for population 1 (main analysis sample of infants for whom a vaginal delivery might be considered) are printed in bold. [a] Multiple pregnancy has not been used as an adjustment factor in models for population 2 and population 3.

cies, lower GA, BW <3rd percentile, male gender, and noncephalic presentation (online suppl. Table 2).

Mode of Delivery and Outcomes

Postnatal variables in both groups of the main analysis sample did not differ in terms of the Apgar score, the use of MV and surfactant, and any maternal breast milk at discharge. Use of CPAP and of supplemental oxygen was more common in infants delivered by C-section, while postnatal PDA therapy with NSAID and application of steroids for BPD or other reasons were more frequently observed in infants after vaginal delivery (Table 1). The overall incidence of BPD did not differ between the vaginal delivery and the C-section group. The mode of delivery also did not impact the composite outcome of death or BPD (Table 2). Restriction of analyses to singleton births (= population 2) and to infants in cephalic presentation (= population 3) rendered identical results (Table 2) as did models using the total cohort (Table 2; online suppl. Table 3). Results for BPD and death or BPD in our main analysis sample were unchanged when the analysis was limited to infants of ≥26+0 weeks gestation to exclude different regions' attitudes toward delivery by C-section in the most immature infants (Table 3). However, a negative effect was observed for vaginal delivery in the full sample, where the number of SGA infants stemming from preeclampsia/hemolysis, elevated liver enzymes, and low platelet count and intrauterine growth restriction was overrepresented in the C-section group (Table 3). Sensitivity analyses investigating infants with severe BPD revealed the identical results similar to the main analyses (online suppl. Table 4). Furthermore, additional risk adjustment for postnatal corticosteroid therapy to treat BPD, PDA therapy with NSAIDs, and provision of any maternal milk at discharge did as well not reveal statistically significant differences between birth by vaginal delivery and C-section (online suppl. Table 5).

Impact of Regional C-Section Rates on the Outcomes

To investigate the impact of regional differences in C-section rates on the outcome variables, the 11 countries were separated into those with <50% and ≥50% C-section rates. C-section was less frequent in the regions of the Netherlands, Estonia, the UK, France, and Belgium and more common in Denmark, Portugal, Poland, Sweden, Italy, and Germany (online suppl. Table 1). As in the previous analyses, the mode of delivery did not affect the overall rate of BPD and the composite outcome of death or BPD (Table 4).

Table 4. Sensitivity analysis in countries with low and high C-section rates

Outcomes	*N*	C-section, *n*/*N* (%)	Vaginal delivery (reference), *n*/*N* (%)	Model 0, mixed effects, crude OR [95% CI]	Model 1, mixed effects, adjusted OR [95% CI]
Population 0					
Low C-section rate					
Death	4,140	199/2,438 (8.2)	226/1,702 (13.3)	0.58 [0.47–0.72]	0.84 [0.59–1.21]
Moderate/severe BPD	3,713	349/2,176 (16.0)	262/1,426 (18.4)	0.88 [0.71–1.08]	0.83 [0.57–1.21]
High C-section rate					
Death	3,295	257/2,582 (9.9)	100/713 (14.0)	0.68 [0.52–0.90]	0.92 [0.62–1.36]
Moderate/severe BPD	2,938	227/2,296 (9.9)	66/607 (10.9)	0.91 [0.66–1.25]	0.81 [0.48–1.38]
Population 1					
Low C-section rate					
Death	**2,573**	**81/1,010 (8.0)**	**204/1,563 (13.1)**	**0.55 [0.42–0.74]**	**0.93 [0.65–1.45]**
Moderate/severe BPD	**2,287**	**126/903 (13.9)**	**241/1,311 (18.4)**	**0.73 [0.55–0.96]**	**0.89 [0.57–1.38]**
High C-section rate					
Death	**1,729**	**106/1,093 (9.7)**	**84/636 (13.2)**	**0.70 [0.50–0.98]**	**0.75 [0.45–1.25]**
Moderate/severe BPD	**1,539**	**75/973 (7.7)**	**54/548 (9.8)**	**0.79 [0.52–1.18]**	**0.73 [0.35–1.52]**
Population 2					
Low C-section rate					
Death	1,685	52/542 (9.6)	144/1,143 (12.6)	0.69 [0.48–0.98]	1.05 [0.61–1.81]
Moderate/severe BPD	1,488	71/477 (14.9)	195/970 (20.1)	0.69 [0.49–1.00]	0.78 [0.44–1.38]
High C-section rate					
Death	1,063	58/537 (10.8)	66/526 (12.5)	0.84 [0.57–1.26]	0.79 [0.43–1.46]
Moderate/severe BPD	939	39/474 (8.2)	45/458 (9.8)	0.83 [0.50–1.38]	1.11 [0.45–2.75]
Population 3					
Low C-section rate					
Death	1,184	21/254 (8.3)	90/930 (9.7)	0.75 [0.44–1.28]	2.03 [0.94–4.36]
Moderate/severe BPD	1,072	30/231 (13.0)	142/821 (17.3)	0.71 [0.44–1.15]	1.23 [0.62–2.44]
High C-section rate					
Death	726	23/255 (9.0)	45/471 (9.6)	0.93 [0.54–1.63]	0.94 [0.45–1.98]
Moderate/severe BPD	658	14/229 (6.1)	40/424 (9.4)	0.67 [0.33–1.36]	0.88 [0.29–2.66]

Analyses from Table 2 were separated for regions with low (<50%; the Netherlands, Estonia, the UK, France, Belgium) and high (>50%; Denmark, Portugal, Poland, Sweden, Italy, Germany) C-section rates. Results for population 1 (main analysis sample of infants for whom a vaginal delivery might be considered) are printed in bold.

Discussion

Our study is a population-based cohort evaluation of the association between mode of delivery and BPD. Using the criteria of supplemental oxygen and/or respiratory support at 36 weeks' GA, these analyses focused on infants with moderate/severe BPD who are at particular risk for clinically relevant lifelong restrictions in lung function. Our results show that the mode of delivery did not impact the incidence of moderate/severe BPD and of severe BPD. As mortality rates between both groups did not differ significantly, carry-over effects of variations in mortality on BPD could be excluded.

In recent years, several risk factors for BPD have been newly identified, including lack of breast milk provision and pathological microbial colonization. Our data indicate that the mode of delivery is not to be added to this list of risk factors contributing to BPD. This might appear surprising as the perinatal period significantly determines the severity of lung disease. Furthermore, microbial colonization and lung fluid clearance after birth are affected by the mode of delivery, and their impact on respiratory status and pathologic microbial colonization is well documented for term neonates. Our detailed analyses do not support the hypothesis that vaginal delivery with improved lung fluid clearance and colonization of the infant with its mother´s microbiota improves pulmonary outcome. Similarly, arguments in favor of delivery by C-section to reduce death or BPD are refuted.

Previous publications from the EPICE cohort have highlighted huge variations in clinical practice across Europe even in areas where there is a clear evidence base

[16]. This is even more marked for areas without conclusive evidence for specific treatments. For example, for PDA treatment, intervention rates ranged from 10% to 39% between regions [17]. Unsurprisingly, the overall analysis did not detect any benefit of PDA therapy on death or BPD. Another example is postnatal steroid policy, where large differences in use were observed after adjustment for patient case-mix. Their restricted use was not associated with a higher risk for BPD in the EPICE cohort [18]. Here, we show that evidence regarding the mode of delivery follows a similar pattern. The frequency of C-section varied between 30.7% in the Netherlands and 77.9% in Germany. These disparities could not be explained by differences in perinatal characteristics between regions and countries but reflect uncertainty about the optimal mode of delivery and national policies and practices. Despite the high importance for the mother and child, the literature on this topic remains sparse and sometimes contradictory. Our results add to the list of studies finding equivalent outcomes of vaginal delivery or C-section [8].

Antenatal steroids, early CPAP, and surfactant therapy reduce respiratory distress after birth, while their impact on BPD remains modest or has not been demonstrated [19–21]. This discrepancy can be explained by the multifactorial origins of BPD where one intervention, even if highly effective in the short term, can only modestly impact BPD. Our results point out that even if there were minor effects of mode of delivery, other factors affecting BPD have outweighed them or mitigated their effects. These results are corroborated by the postnatal respiratory parameters studied. We detected no differences in the postnatal need for MV and surfactant therapy between infants with vaginal and C-section delivery (Table 1).

We decided to use the most widely used NICHD consensus definition to allow comparability with other studies and to specify the relevance of mode of delivery for severe BPD as these infants have the highest risk for lifetime sequelae. Congruent results for the need for respiratory interventions after birth and BPD argue against intensive research investments or investigations on the mode of delivery and pulmonary outcome in very preterm infants. In our cohort, the frequency of BPD was slightly lower than observed in the preceding MOSAIC cohort study performed in 2003, but it was within the wide range reported from other cohorts [1, 22]. As expected from the nature of preterm birth, infants eligible for a vaginal delivery were not equally distributed between both groups. To account for these disparities, we not only excluded cases with a very high probability of C-section as done in previous EPICE investigations but also reproduced results on the total population. We used hierarchical models for taking into consideration clustering and modeling differences between units as random effects. Further restrictions of the study population were included to study those infants that had comparable prerequisites to consider a spontaneous delivery. Furthermore, we took into consideration the impact of mortality on BPD rates through the composite outcome of death or BPD. Due to the disparities of perinatal characteristics between the two groups and the different attitudes toward C-section and respiratory therapy between units and regions, we tested our hypothesis on different populations based on their levels of risk adjustment in our statistical models. Thereby, through adjustment and stratification, we were able to take into account a large number of acknowledged risk factors for BPD.

Strengths and Limitations of the Study

The major strengths of our analyses are the population-based approach within 19 different regions across 11 countries in Europe, enabling generalizability of results, the prospective design, and the use of preset protocols for data collection and analyses. The retrospective classification of infants for whom a vaginal delivery could be considered needs to be acknowledged as one limitation of our analysis that may have led to misclassification of some cases. Reassuringly, however, our results were similar in the full sample. We were not able to include the details of other factors influencing BPD like nicotine exposure, nutritional supply, caffeine therapy, and nosocomial infections that vary between units and regions [23–25]. As we took into consideration unit and region in our models, it is though unlikely that one of these factors would reverse the overall results.

Implications for Practice and Policies

Preterm infants, particularly extremely and very low BW infants, are increasingly delivered by C-section [26]. This may be due to concerns about their high vulnerability and risk for acute morbidities that affect their long-term outcome and especially psychomotor development. However, the combined analyses of all available data on this topic do not suggest that a systematic practice of C-section is superior to vaginal delivery despite isolated reports of benefit [8, 10]. Furthermore, the maternal risks of C-section on subsequent reproductive health need to be acknowledged [27]. Our findings add novel evidence on this topic and suggest that in situations of impeding

preterm delivery where a vaginal delivery can be considered, the outcomes of BPD and death or BPD do not justify the preference for delivery by C-section.

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Statement of Ethics

Ethics approval was obtained in each region from regional and/or hospital Ethics Committees as required by national legislation. The European study was additionally approved by the French Advisory Committee on Use of Health Data in Medical Research (CCTIRS No. 13.020 on January 24th, 2013) and the French National Commission for Data Protection and Liberties (CNII No. DR-2013-194 on April 10th, 2013). Active or passive informed parental consent was obtained as required by national legislation of participating countries.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Principal investigator: Jennifer Zeitlin; study design, interpretation of the data, and writing group of the manuscript: Harald Ehrhardt, Rolf F. Maier, and Jennifer Zeitlin; full access to the study datasets and responsibility for the accuracy of the data analyses: Thomas Desplanches and Jennifer Zeitlin; critical revision of the manuscript for important intellectual content and approval of the final version of the manuscript: all the authors and all members of the EPICE research group.

Data Availability Statement

Access to data in the EPICE cohort is currently not possible for researchers who are not members of the consortium, but EPICE is part of a H2020 project (RECAP, https://recap-preterm.eu/) to develop a platform for data sharing. The corresponding author is available for more information.

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