Changes in Neonatal Morbidity and Neonatal Care Practices of Infants Born Very Preterm in the Netherlands in the 1980s and 2000s

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Abstract

This study evaluates changes in neonatal morbidity and care practices of very preterm (VP) infants born in the Netherlands in the 1980s and 2000s and analyzes whether these changes were associated with infant and maternal characteristics, risk factors during pregnancy, and obstetrical outcomes.

The community-based cohorts of POPS (1983) and LOLLIPOP (2002-03) provided perinatal data for the study. The analysis enrolled 1,228 participants born VP (before 32 weeks of gestation) and survived to 2 years of age. In 2003, mothers were on average 3.3 years older when giving birth than in 1983. Multiple birth rates increased by 50% and significantly more parents had higher education.

Prevalence of severe IVH and sepsis decreased in VP infants between 1983 and 2003. LOLLIPOP infants received more often continuous positive airway pressure (CPAP), mechanical ventilation, and caffeine therapy than POPS infants. Antenatal corticosteroids and surfactant therapy were introduced only in the LOLLIPOP cohort. In 2002-03, length of stay in the NICU was reduced by 57% in LOLLIPOP (median 16 days) compared to POPS (median 38 days). LOLLIPOP infants also spent 11 days less total time in hospital after birth (median 54 days). This is a reduction of 17% compared to POPS (median 65 days). Differences persisted after adjustment for infant and maternal characteristics, risk factors during pregnancy, and obstetrical outcomes.

Conclusions: Infant and mother characteristics changed considerably as well as obstetric and neonatal care practices. Outcomes of several severe neonatal morbidities improved. Length of NICU and hospital stay were significantly shorter in the 2000s.

Summary

What is known

Perinatal care practices provided for infants born very preterm (VP) and survival rates of VPs have improved since the 1980s. Social and demographic factors have also changed over the last decades.

What is new

This study adds that for surviving VP infants, significant decreases of severe morbidities such as severe intraventricular hemorrhage and sepsis are found in the Netherlands for two cohorts born 20 years apart. It shows significant changes in respiratory therapy, reduction of time in the NICU (by 22 days, 57%) and total hospital stay (by 11 days, 17%).

Introduction

Very preterm (VP) birth before 32 weeks of gestation is a significant public health concern globally associated with16 high rates of mortality as well as short- and long-term morbidities [1]. It may result in neurodevelopmental, behavioural, and organ-specific health problems persisting throughout childhood and even for the whole lifespan [2]. All sequelae of preterm birth put a high burden on the family of the child, the

health system and society [1]. There is consistent evidence that mortality has decreased in recent years, mainly in the group of extremely low birth weight/extremely preterm infants and at the limits of viability [3]–[7]. Several studies published data on morbidity for cohorts being recruited up to twenty years apart. Most of them report an increase in infants surviving without major morbidities [3]–[6]. Mixed outcome results were observed for single major morbidities like bronchopulmonary dysplasia (BPD), severe intraventricular haemorrhage (IVH), early and late-onset sepsis, severe retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) or patent ductus arteriosus (PDA) [3]–[9].

Improved survival and health outcomes of VP infants has been observed in the last decades. This fact might be explained by changes in obstetric and neonatal/pediatric care practices [3]–[5], such as the implementation of prenatal steroids for induction of foetal lung maturation given to women at risk for very preterm delivery. The use of antenatal corticosteroids not only reduced mortality rates, but also resulted in fewer neonates suffering from respiratory distress syndrome and IVH [10]. Caesarean section became a more common practice, specifically for the delivery of extremely preterm infants [9], [10]. Postnatal care introduced nasal continuous positive airway pressure (CPAP), new ventilation techniques and most importantly the intratracheal application of surfactant [9], [10].

However, not only obstetric and neonatal care has changed, but there may also be changes in social conditions such as better educated mothers living in improved social circumstances and improved healthy lifestyles such as fewer mothers smoking. Social factors have been found to be associated with both pre- and neonatal morbidities and infant outcome [11], [12].

Evidence that neonatal morbidity still varies considerably across different regions in Europe [13], [14] underlines the need to compare data at a national level from cohorts recruited more than a decade apart. For this purpose, we conducted a comparison of two community-based cohorts only within one country, namely the Netherlands: POPS (1983) and LOLLIPOP (2002–2003). Between the 1980s and 2000s, three new policies and acts have been passed and implemented in neonatal care in the Netherlands. First, new modalities such as antenatal corticosteroids, surfactant therapy and high frequency ventilation were introduced [15]. Second, the Act of Ministry of Health [16] assigned 10 centres for neonatal intensive care treatment and the Health Council [17] recommended obstetrical staff to transfer pregnant women with risk of premature birth to perinatal centres. Third, the care of extremely preterm newborn infants was conservative before the 2000s [18] in terms that the obstetrical guideline focused on the prolongation of pregnancy and not an increase of live-birth. Intensive neonatal treatment was only recommended for infants born < 26 weeks since 2005 [19].

Based on a unique policy background in the Netherlands, POPS and LOLLIPOP provide an opportunity to assess changes in neonatal outcomes and treatments during a period of 20 years with important general and country-specific changes in neonatal care. Therefore, this study aims to identify changes in neonatal morbidity and neonatal care practices of infants born VP between the 1980s and 2000s in the Netherlands and whether these changes were associated with infant and maternal characteristics and risk factors during pregnancy and obstetrical outcomes.

Methods

Study design

This is an observational study using data collected during the neonatal period in two Dutch cohorts of VP infants from 1983 (POPS) and 2002-03 (LOLLIPOP). This study followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guideline for reporting cohort studies [20]. The cohort data were made available using data transfer agreements between the partners.

Study populations

POPS cohort (1983)

The POPS-cohort (Project on Preterm and Small for gestational age infants) comprised 1,338 VP and/or very low birth weight (VLBW, < 1,500 grams) infants who were live-born in the Netherlands between January 1 and December 31, 1983. Eighty-five infants, who met the inclusion criteria, were not included because they were born in non-participating hospitals. The study population, therefore, consisted of 94% of all eligible infants in the Netherlands [21].

The pediatricians of neonatal units of the participating hospitals completed an extensive, standardized, pre-coded list of perinatal data until discharge [15].

LOLLIPOP cohort (2002–2003)

The Longitudinal Preterm Outcome Project (LOLLIPOP) is a community-based cohort including preterm and full-term children, born in 2002 and 2003 [22], [23]. Thirteen preventive child healthcare centres (PCHCs) participated in the study. All children assigned to the last PCHC visit at age 43–49 months and born < 37 weeks GA were included (approximately 25% of this age group population). The cohort was enriched with VP children born in 2003 from 5 NICUs who were alive at follow-up. Children with major congenital malformations were excluded. Of the 2,963 eligible children, 1,983 participated in LOLLIPOP. For the present study we included all VP children within this cohort of whom perinatal and neonatal data were collected and of whom developmental milestones had been recorded by PCHC professionals (N = 697). Perinatal and neonatal data were collected from registered data from various sources, including a general parental questionnaire, birth registers, PCHC records, and medical records of both mother and child, allowing cross-checking of information.

Medical Ethic Committees of the participating hospitals approved the study protocol for POPS [21], and the Medical Ethic Committee of the University Medical Centre Groningen approved the study protocol for LOLLIPOP [22]. Parents gave written informed consent.

Harmonized outcomes

Perinatal data was harmonized retrospectively following the RECAP preterm harmonization guideline [24] as well as other sources reporting harmonization techniques [25], [26]. First, a set of target variables relevant to the research questions was defined (Supplementary File 1). Second, definitions, value units and variable categories were checked regarding adequacy and possible concordance or showing overlap with the definition of the variables of the other cohort. Third, variables were put into three categories depending on

their eligibility for harmonization. After generating a joint harmonized data set, descriptive statistics were calculated and variables with large percentages of missing data (> 40%) were excluded from analyses. Table 1 comprises the variables harmonized for the comparison analysis.

Table 1
Variable harmonized for the comparison analysis.

Factors potentially affecting outcomes		**Outcomes**	
Infant and maternal characteristics	**Prenatal risk factors and obstetrical outcomes**	**Neonatal morbidity**	**Neonatal care practices**
Infant • GA • BW • SGA • sex • multiples **Mother** • age at birth • parental education	**Prenatal risk factors**: • previous birth • smoking during pregnancy **Obstetrical outcomes** • cesarean section • PPROM • meconium-stained amniotic fluid • breech presentation • APGAR at 5 minutes < 7	• IVH grade III-IV • proven NEC • sepsis • apnea	• mechanical ventilation • CPAP • caffeine therapy • postnatal corticosteroids • length of mechanical ventilation • length of stay in NICU • length of stay in hospital

GA: gestational age, BW: birth weight, SGA: small for gestation, PPROM: premature rupture of membranes, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, CPAP: continuous positive airway pressure, NICU: neonatal intensive care unit

Statistical analysis

In order to have two comparable groups of participants, we had to exclude some individuals from both cohorts for the present analysis. Included and excluded infants from the cohorts (s. Figure 1) were compared applying independent t-test for continuous variables and chi-square test for categorical variables. All variables used in the present analysis were tested for differences between eligible and non-eligible POPS infants. Included and excluded LOLLIPOP infants were tested for differences in GA, BW, sex, multiple and previous pregnancy.

To test for differences between cohorts on neonatal morbidity and neonatal care practices, multiple negative binomial regression models were performed for continuous variables without normal distribution [27] and multiple logistic regression models for dichotomous variables. Adjusted models included covariates, such as infant and maternal characteristics, prenatal risk factors and obstetrical outcomes. Regression models of difference in NICU stay and hospital stay were adjusted additionally for all neonatal morbidity and care practices used in the study.

Analyses were based on participants with non-missing values on covariates and outcomes. A p-value of < 0.05 was considered as statistically significant; in case of multiple testing the p-value was Bonferroni corrected. The statistical software packages SPSS 27.0 (IBM SPSS for Windows) and Stata 16.1 (Statacorp. Stata Statistical Software) were used for calculation.

Results

Participants: harmonization of the two cohorts

As POPS collected infants born VP (< 32 weeks GA) or VLBW (< 1500 grams) and LOLLIPOP included only infants < 32 weeks GA, we applied joint inclusion criteria for the present analysis: 1) GA at birth < 32 weeks, 2) absence of any severe congenital malformations 3) survival up to 2 years, 4) complete perinatal data. Figure 1 provides an overview how participants of both cohorts were selected.

The final data set comprised N = 679 infants from POPS and N = 549 from LOLLIPOP.

POPS children who died before 24 months of age were born more often at lower GA, BW, APGAR score, were multiples, in breech presentation and without caesarean section than survivors (data not shown). Deceased children had more often severe IVH and received more often mechanical ventilation, but less often CPAP (data not shown).

In LOLLIPOP, parent's not granting permission for retrospective analysis of perinatal data and previous excluding (N = 85) or difficulties in retrieving neonatal medical records (N = 63) resulted in 148 children without neonatal data. These children were excluded from the present analysis. Excluded children were not significantly different to those remaining in the final sample regarding GA, BW, sex, multiple birth (data not shown). However, mothers of excluded children reported more previous pregnancies than the mothers of the included group (40.9% vs 26.2%, chi2(1) = 11.12, p < 0.01).

Description of the cohorts

Infant and maternal characteristics

Table 2 provides descriptive parameters for the two cohorts on infant and maternal characteristics. There were no differences in GA, birth weight (BW), SGA and sex, but LOLLIPOP mothers were more highly educated and older at birth than POPS mothers. More LOLLIPOP mothers gave birth to multiples.

Table 2
Comparison analysis between cohorts on infant and maternal characteristics using t-test or chi-square test with Bonferroni correction

	LOLLIPOP N = 549		POPS N = 679			p-value
Infant characteristics						
	Mean	**SD**	**Mean**	**SD**	**T-value (df)**	
Gestational age, weeks	29.2	1.6	29.4	1.5	1.8 (1226)	0.07
Birth weight, grams	1298.2	367.4	1329.2	315.5	1.6 (1226)	0.11
	N	**%**	**N**	**%**	**Chi^2 (df)**	
SGA	104	18.9	110	16.2	1.6 (1)	0.21
Sex, male	265	48.3	363	53.9	0.6 (1)	0.55
Multiples	187	34.1	156	23.0	18.5 (1)	< 0.001*
Maternal characteristics						
	Mean	**SD**	**Mean**	**SD**	**T-value (df)**	
Maternal age at birth, years	30.5	4.5	27.2	4.7	9.18 (363)	< 0.001*
	N	**%**	**N**	**%**	**Chi^2 (df)**	
Parental education, high	227	41.9	158	25.4	64.8 (2)	< 0.001*
* significant after Bonferroni adjusted						
In POPS, missing data ranged between 0 and 57. In LOLLIPOP, missing data ranged between 0 and 10, but the variable of maternal age comprised N = 211 complete data.						

Prenatal risk factors and obstetrical outcomes

Table 3 summarizes the differences in the prenatal risk factors for prematurity and obstetrical outcomes between cohorts. Less mothers from LOLLIPOP reported smoking during pregnancy and previous births. However, the difference in smoking rates was rendered non-significant when results were adjusted for maternal characteristics (Model 3). Caesarean section was more frequent in LOLLIPOP and adverse obstetrical outcomes such as preterm rupture of membranes (PPROM), meconium stained amniotic fluid and low AGPAR score at 5 minutes were more frequent in POPS. Differences remained stable even after adjusting for infant and maternal characteristics.

Table 3
Differences in prenatal risk factors for prematurity and obstetrical outcomes of VP infants from the Netherlands. Unadjusted and adjusted cohort effects: odds ratios (OR) of likelihood for LOLLIPOP (2002–2003) vs. POPS (1983) cohorts

	LOLLIPOP N = 549		POPS N = 679		Effect of cohort (LOLLIPOP vs POPS)		
					Model 1	Model 2	Model 3
	N	%	N	%	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Prenatal risk factors							
Previous birth	144	26.2	383	56.5	0.27 (0.21–0.35)***	-	0.03 (0.10–0.22)***
Maternal smoking during pregnancy	112	20.5	190	31.4	0.56 (0.43–0.74)***	-	0.94 (0.63–1.39)
Obstetrical outcomes							
Full course of antenatal corticosteroids	293	53.4	-	-	-	-	-
Caesarean section	282	53.1	242	35.6	2.05 (1.62–2.58)***	2.23 (1.73–2.88)***	2.05 (1.42–2.94)***
PPROM	95	17.9	163	24.0	0.69 (0.52–0.92)*	0.71 (0.53–0.95)*	0.59 (0.39–0.91)*
Meconium stained amniotic fluid	12	2.3	33	5.0	0.44 (0.23–0.86)*	0.47 (0.24–0.92)*	0.13 (0.02–0.95)*
Breech presentation	124	36.3	187	27.5	1.50 (1.16–1.95)**	1.37 (1.05–1.79)*	0.97 (0.65–1.45)
APGAR < 7 at 5 minutes	46	8.7	80	13.4	0.62 (0.42–0.90)*	0.63 (0.42–0.93)*	0.47 (0.25–0.88)*
Model 1: unadjusted							
Model 2: adjusted for infant characteristics (gestational age, small for gestation, multiple birth, sex)							
Model 3 adjusted for infant and maternal characteristics (gestational age, small for gestation, multiple birth, sex, maternal age at birth, parental education)							
*** p < 0.001 **p < 0.01 *p < 0.05							
Prenatal risk factors were adjusted only for maternal characteristics (maternal age at birth, parental education)							
In POPS, missing data ranged between 0 and 84. In LOLLIPOP, missing data ranged between 0 and 18, but the variable of breech presentation comprised N = 424 complete data.							

Main outcomes

Neonatal morbidity and neonatal care practices

First, we investigated the unadjusted differences in neonatal morbidity and neonatal care practices between cohorts (s. Table 4 – Model 1). Except for proven NEC, observed unadjusted differences indicated that LOLLIPOP infants had less frequently severe IVH and sepsis, but more frequently apnoeic events than POPS infants. We found that LOLLIPOP infants were more likely to receive mechanical ventilation, CPAP and caffeine therapy. Though more infants were treated with mechanical ventilation in LOLLIPOP, the length of ventilation remained unchanged between the two time periods. Duration of stay in the NICU was reduced for 57% in LOLLIPOP (median 16 days) compared to POPS (median 38 days). LOLLIPOP infants also spent 11 days less total time in hospital after birth. This is a reduction of 17% compared to POPS.

Table 4

Differences in neonatal morbidity and care practices of VP infants from the Netherlands. Unadjusted and adjusted cohort effects: odds ratios (OR) of likelihood or incidence rate ratio (IRR) for LOLLIPOP (2002–2003) vs. POPS (1983) cohorts

	LOLLIPOP N = 549		POPS N = 679		Effect of cohort (LOLLIPOP vs POPS)			
					Model 1	Model 2	Model 3	Model 4
	N	%	N	%	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Morbidity								
IVH grade III-IV	18	3.6	47	9.3	0.36 (0.21–0.63)***	0.31 (0.17–0.56)***	0.14 (0.04–0.47)**	0.26 (0.06–1.12)
sepsis	135	27.7	246	36.3	0.67 (0.52–0.87)**	0.61 (0.47–0.80)***	0.57 (0.38–0.84)**	0.53 (0.32–0.88)*
proven NEC	12	2.3	11	1.6	1.42 (0.62–3.23)	1.45 (0.63–3.35)	1.49 (0.40–5.56)	2.22 (0.45–11.10)
apnea	465	90.8	453	66.9	4.89 (3.48–6.87)***	4.90 (3.44–6.99)***	7.13 (4.03–12.61)***	10.52 (5.18–21.37)***
Care practices								
Surfactant therapy	191	34.8	-	-	-	-	-	-
mechanical ventilation	291	55.7	302	47.0	1.42 (1.13–1.79)**	1.40 (1.09–1.80)**	1.29 (0.90–1.85)	1.52 (0.96–2.42)

Model 1: unadjusted

Model 2: adjusted for infant characteristics (gestational age, small for gestation, multiple birth, sex)

Model 3 adjusted for infant and maternal characteristics (gestational age, small for gestation, multiple birth, sex, maternal age at birth, parental education)

Model 4: adjusted for infant, maternal characteristics, prenatal risk factors and obstetrical outcomes (gestational age, small for gestation, multiple birth, sex, maternal age at birth, parental education, maternal smoking during pregnancy, previous pregnancy, cesarean section, meconium, PPROM, breech presentation, low APGAR)

*** $p < 0.001$ **$p < 0.01$ *$p < 0.05$

In POPS, missing data ranged from N = 0 to N = 52, but the variable of IVH comprised N = 505 complete data, and the variable of length of NICU stay N = 454. In LOLLIPOP, missing data ranged from N = 23 to N = 87.

	LOLLIPOP N = 549		POPS N = 679		Effect of cohort (LOLLIPOP vs POPS)			
CPAP	438	83.9	305	46.9	5.90 (4.46–7.80)***	6.31 (4.71–8.45)***	7.71 (4.94–12.10)***	7.88 (4.64–13.37)***
caffeine therapy	452	89.3	402	64.1	4.69 (3.38–6.49)***	4.82 (3.43–6.76)***	5.88 (3.50–9.89)***	7.93 (4.26–14.77)***
postnatal corticosteroids	28	5.5	49	7.2	0.75 (0.46–1.20)	0.60 (0.36-1.00)	0.42 (0.18–1.01)	0.54 (0.19–1.57)
	Median	**Range**	**Median**	**Range**	**Model 1 IRR (CI 95%)**	**Model 2 IRR (CI 95%)**	**Model 3 IRR (CI 95%)**	**Model 4 IRR (CI 95%)**
length of mechanical ventilation, days	1	0–84	0	0–78	1.15 (0.91–1.46)	0.88 (0.71–1.10)	0.87 (0.62–1.24)	0.92 (0.58–1.46)
length of NICU stay, days	16	0-143	38	0-380	0.48 (0.44–0.54)***	0.41 (0.38–0.45)***	0.41 (0.36–0.47)***	0.39 (0.33–0.46)***
length of hospital stay, days	54	10–339	65	12–380	0.86 (0.82–0.90)***	0.82 (0.79–0.85)***	0.86 (0.82–0.91)***	0.89 (0.83–0.94)***
Model 1: unadjusted								
Model 2: adjusted for infant characteristics (gestational age, small for gestation, multiple birth, sex)								
Model 3 adjusted for infant and maternal characteristics (gestational age, small for gestation, multiple birth, sex, maternal age at birth, parental education)								
Model 4: adjusted for infant, maternal characteristics, prenatal risk factors and obstetrical outcomes (gestational age, small for gestation, multiple birth, sex, maternal age at birth, parental education, maternal smoking during pregnancy, previous pregnancy, cesarean section, meconium, PPROM, breech presentation, low APGAR)								
*** p < 0.001 **p < 0.01 *p < 0.05								
In POPS, missing data ranged from N = 0 to N = 52, but the variable of IVH comprised N = 505 complete data, and the variable of length of NICU stay N = 454. In LOLLIPOP, missing data ranged from N = 23 to N = 87.								

Second, this study also aims to detect the differences in neonatal morbidity and neonatal care practices between cohorts when outcomes were adjusted for infant (Model 2) and maternal characteristics (Model 3), prenatal risk factors and obstetrical outcomes (Model 4). Odds ratios (OR) for severe IVH, apnoea and sepsis remained, but confidence intervals increased in the adjusted models. The differences in neonatal care

practices over time remained for rate of CPAP and caffeine therapy after adjustment for infant and maternal characteristics, prenatal risk factors and obstetrical outcomes. Length of NICU stay and hospital stay was also analysed with adjustment for all neonatal morbidity and care: OR: 0.37, 95% CI [0.31–0.45], $p < 0.001$ and OR: 0.86, 95% CI [0.80–0.92], $p < 0.001$, respectively. Adjustments did not change the significant differences in length of NICU and hospital stay.

Discussion

We assessed changes twenty years apart in neonatal morbidity and neonatal care practices of infants born VP in 1983 and 2002–2003 in the Netherlands, and tested if these changes were attributed to different infant and maternal characteristics as well as risk factors during pregnancy and obstetrical outcomes. Significant differences in neonatal morbidity and neonatal care practices between POPS and LOLLIPOP cohorts were found. The rate of severe IVH and sepsis were lower and administration of CPAP and caffeine therapy increased in the LOLLIPOP compared to POPS. In the 2000s, VP infants were treated for a shorter time in the NICU and discharged earlier from hospital. These differences persisted even after adjustment for relevant infant, maternal and obstetrical factors.

Neonatal morbidity

This study revealed that prevalence of severe IVH and sepsis decreased in VP survivors over two decades. Previous reports from the Netherlands comparing the prevalence of severe IVH in the 1990s and the 1980s did not find declining IVH rates [28]–[30]. Antenatal administration of corticosteroids routinely given to mothers with a risk of premature delivery may thus play a significant role in reducing IVH rates [10]. The significant decrease in the sepsis rate after adjustment might be a consequence of increasing antibiotic therapy during pregnancy and prophylactic antibiotic treatment after birth until the absence of an infection was proven, but no data on these treatments were collected in POPS and LOLLIPOP.

The diagnosis of apnoea increased significantly from 66.9% (POPS) to 90.8%. This may be due to the increased use of CPAP (see Neonatal care practices section).

No significant difference was observed for the rate of proven NEC. Up to now most therapeutic strategies to reduce the rate of NEC in this population have failed [31]–[33].

Because of the different definitions for BPD used in both cohorts (diagnosis at postnatal 28 days versus 36 weeks postmenstrual age), this study could not analyse BPD data. From the factors associated with the prevalence of BPD, only the duration of mechanical ventilation was documented here which remained constant between 1983 and 2003. On the other hand, this result cannot confirm or refuse the findings of other studies conducted in Europe and reporting prevalence of over 40% of BPD in the 2000s [34]–[36].

Neonatal care practices

We found increased use of respiratory support (CPAP, mechanical ventilation) and caffeine therapy in the LOLLIPOP cohort. Therapies accelerating lung maturation and supporting lung function were administered only in LOLLIPOP (and not in POPS) at a proportion of 53.4% for complete antenatal corticosteroid treatment

and 37.8% receiving surfactant therapy. The rate of surfactant therapy is in line with [6] or below the average proportion of other findings from the 2000s [5], [8]. Other studies reported both complete and incomplete steroid treatments received by the mother [8], [37] which can explain the lower proportion of full course of antenatal corticosteroids administered in LOLLIPOP. There is good evidence that four neonatal care practices, namely treatment in NICU, administration of antenatal corticosteroids, prevention of hypothermia, and surfactant applied within two hours after birth or early nasal CPAP can result in survival with less severe morbidity for infants at high risk [38]. This study was not designed to compare these essential practices because they were not routinely applied in the 1980s.

The lower proportion of postnatal corticosteroids administered in 2000 years corresponds to other findings [5] and might be related by a new guideline on more moderate use due to their major adverse long-term effect on health and neurodevelopment [39].

This study discovered a significant decline in the length of NICU and total hospital stay after VP birth in 2002–2003. This difference remained significant after adjustment for neonatal care practices. Thus, the study does not confirm that the length of NICU and hospital stay is closely connected to neonatal care practices analysed here.

Prenatal risk factors for prematurity and obstetrical outcomes

The decline of maternal smoking during pregnancy from 31.4% (POPS) to 20.5% (LOLLIPOP) may be expected, as daily smoking of Dutch adults decreased from 40% in 1983 to 26.7% in 2003 [40]. Despite the general trend of total fertility rate increasing from 1.47 to 1.75 between 1983 and 2003 in the Netherlands [41]. we observed a decline in parity (more first mothers) in LOLLIPOP.

We found improved obstetrical outcomes of infants born in the 2000s for the rate of PPROM, meconium contained amniotic fluid and low APGAR score compared to POPS infants. This may be attributed to improved pregnancy care. The prevalence of caesarean section increased over time which fits into the international trends [42].

Infant and mother characteristics

The cohorts were comparable regarding infant characteristics such as GA, BW, sex and SGA infants. In both cohorts, the prevalence of infants born < 26 weeks GA was under 2 %. This phenomenon can be attributed to the fact that policy on treatment of VP infants was still conservative at the beginning of the 2000s in the Netherlands with neonatal intensive care not routinely provided to infants born < 26 weeks GA [18].

The number of multiples was higher in the LOLLIPOP cohort. This is in line with a general trend of increased multiple birth associated with increased use of assisted reproductive technologies with multiple embryos being implanted [10] and the increasing age of the mothers [43]. The increase of mean maternal age from 27.2 to 30.5 years and the higher parental education in LOLLIPOP can be explained by a general sociodemographic trend in Western Europe [44].

Strengths and limitations

As a strength, this study compared data collected in the same country at two time points with a considerable difference of 20 years. The two cohorts represent a sizeable proportion of VP infants in the Netherlands in the respective years (POPS 94%, LOLLIPOP: 25%). Study participants stemmed from the same country with the same population background. The study analysed data of VP infants who survived at least until 2 years of age. We followed a rigorous protocol for the harmonization of the variables prepared for the comparison analysis.

Limitations are the differences of the two cohorts in their research goals and data collection methods. LOLLIPOP is a cross-sectional study of 4-year-old children with retrospective data collection of perinatal and other follow-up data. This resulted in missing data, e.g. prevalence of mortality and major diseases leading to early death or long-term disabilities. Due to the strict harmonization protocol, several important parameters had to be excluded from the analysis, e.g. BPD and maternal diabetes due to diverse definitions. We had to work with limited data of perinatal care practices and for some important therapies such as duration of antibiotic therapy and the establishment of intermediate care unit data was not available. The cohorts did not provide detailed information about the administration protocol of some care practices e.g. for starting and ending CPAP-therapy. Perinatal data of VP infants were demonstrated in this study as examples and thus, the comparison of both cohorts does not provide a whole picture of changes of the medical and social characteristics of VPs over time.

Implications for further research

Studying long term outcomes of cohorts over larger time periods, and even into adulthood, is of high relevance. To gain a deeper insight into the mechanisms of the early developmental origins of adult-onset diseases [45], it is necessary to have study comparisons on the basis of harmonized neonatal morbidity and care practices.

With regard to neonatal morbidity and care, there is a high need for further elaborated clinical and epidemiological studies providing better understanding of the implications of neonatal pathophysiological processes and improvement of therapy. Next data collections should implicate core measures and identical definitions to ensure the comparability between samples [46], [47].

Conclusions

This comparative study of two VP cohorts from 1983 and from 2002-03 in the same country found significant changes in rates of IVH, sepsis, apnoea, CPAP, caffeine therapy and in the length of NICU and hospital stay. Although, studies investigating changes in neonatal morbidity with changes in neonatal care need to consider the significant sociodemographic changes of populations over time. This study did not find a strong correlation between neonatal outcomes and sociodemographic factors. Altered therapeutic approaches might have led to less cases of severe IVH and sepsis. Improved neonatal care practices including antenatal corticosteroids, surfactant therapy and improved respiratory support may have contributed to the economically important reduction in NICU stay (minus 50%) and total hospital stay (minus 15%).

List Of Abbreviations

BPD bronchopulmonary dysplasia

BW birth weight

CPAP continuous positive airway pressure

GA gestational age

IVH intraventricular hemorrhage

LOLLIPOP Longitudinal Preterm Outcome Project

NEC necrotizing enterocolitis

NICU neonatal intensive care unit

PCHC preventive child healthcare center

PDA patent ductus arteriosus

PPROM prolonged premature rupture of membranes

POPS Project on Preterm and Small for gestational age infants

ROP retinopathy of prematurity

SGA small for gestational age

VP very preterm

Declarations

Study funding

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Conflicts of interest

The authors report no conflict of interest.

Availability of data

Data requests can be submitted to the cohort coordinators (POPS: SP; LOLLIPOP: AFB) who will evaluate this request. Metadata of the POPS cohort data is also available on the RECAP data platform (https://recap-preterm.inesctec.pt/cat).

Code availability

SPSS and STATA syntax requests for the current analysis can be submitted to reka.sexty@uni-graz.at

Authors' contributions

Réka E. Sexty, Sylvia van der Pal, Sijmen A. Reijneveld, Arend F. Bos, Dieter Wolke, Stef van Buuren, Peter Bartmann were involved in the study design; Réka E. Sexty, Sylvia van der Pal, Sijmen A. Reijneveld, Arend F. Bos, Leonhard A. Bakker and Guido Lüchters in data management and data analysis; Réka E. Sexty and Peter Bartmann in writing the manuscript. All authors critically revised the manuscript, read and approved the final version.

Ethics approval

Medical Ethics Committees of the participating hospitals of POPS (1983) approved the study protocol, and the LOLLIPOP study (2002-03) was approved by the Medical Ethical Committee of the University Medical Centre Groningen.

Consent for publication

All co-authors have given their consent for publication.

Consent to participate

All parents of POPS and LOLLIPOP participants signed an informed consent form.

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References

1. S. Chawanpaiboon *et al.*, "Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis," *Lancet Glob. Heal.*, vol. 7, no. 1, pp. e37–e46, 2019, doi: 10.1016/S2214-109X(18)30451-0.
2. S. Saigal and L. W. Doyle, "Preterm Birth 3 An overview of mortality and sequelae of preterm birth from infancy to adulthood," *Lancet*, vol. 371, pp. 261–269, 2008.
3. P. Y. Ancel *et al.*, "Survival and morbidity of preterm children born at 22 through 34weeks' gestation in france in 2011 results of the EPIPAGE-2 cohort study," *JAMA Pediatr.*, vol. 169, no. 3, pp. 230–238, 2015, doi: 10.1001/jamapediatrics.2014.3351.
4. A. J. D. Horbar and J. H. Carpenter, "Mortality and Neonatal Morbidity Among Infants 501 to 1500 Grams From 2000 to 2009," *Pediatrics*, vol. 129, no. 6, pp. 1019–1026, 2012, doi: 10.1542/peds.2011-3028.
5. B. J. Stoll *et al.*, "Trends in care practices, morbidity, and mortality of extremely preterm Neonates, 1993-2012," *JAMA - J. Am. Med. Assoc.*, vol. 314, no. 10, pp. 1039–1051, 2015, doi:

10.1001/jama.2015.10244.

6. C. Rüegger, M. Hegglin, M. Adams, and H. U. Bucher, “Population based trends in mortality, morbidity and treatment for very preterm- and very low birth weight infants over 12 years,” *BMC Pediatr.*, vol. 12, 2012, doi: 10.1186/1471-2431-12-17.
7. K. Lui *et al.*, “Trends in Outcomes for Neonates Born Very Preterm and Very Low Birth Weight in 11 High-Income Countries,” *J. Pediatr.*, 2019, doi: 10.1016/j.jpeds.2019.08.020.
8. A. A. Fanaroff *et al.*, “Trends in neonatal morbidity and mortality for very low birthweight infants,” *Am. J. Obstet. Gynecol.*, vol. 196, no. 2, pp. 147.e1-147.e8, 2007, doi: 10.1016/j.ajog.2006.09.014.
9. I. D’Apremont *et al.*, “Trends in Perinatal Practices and Neonatal Outcomes of Very Low Birth Weight Infants during a 16-year Period at NEOCOSUR Centers,” *J. Pediatr.*, vol. 225, pp. 44-50.e1, 2020, doi: 10.1016/j.jpeds.2020.05.040.
10. J. D. Horbar *et al.*, “Trends in Mortality and Morbidity for Very Low Birth Weight Infants, 1991-1999,” *Pediatrics*, vol. 110, no. 1, pp. 143–151, 2002, doi: 10.1542/peds.110.1.143.
11. D. Wolke, S. Johnson, and M. Mendonça, “The Life Course Consequences of Very Preterm Birth,” *Annu. Rev. Dev. Psychol.*, vol. 1, no. 1, pp. 69–92, 2019, doi: 10.1146/annurev-devpsych-121318-084804.
12. I. Benavente-Fernández *et al.*, “Association of Socioeconomic Status and Brain Injury With Neurodevelopmental Outcomes of Very Preterm Children,” *JAMA Netw. open*, vol. 2, no. 5, p. e192914, 2019, doi: 10.1001/jamanetworkopen.2019.2914.
13. J. Zeitlin *et al.*, “Variation in term birthweight across European countries affects the prevalence of small for gestational age among very preterm infants,” *Acta Paediatr. Int. J. Paediatr.*, vol. 106, no. 9, pp. 1447–1455, 2017, doi: 10.1111/apa.13899.
14. A. K. Edstedt Bonamy *et al.*, “Wide variation in severe neonatal morbidity among very preterm infants in European regions,” *Arch. Dis. Child. Fetal Neonatal Ed.*, 2018, doi: 10.1136/archdischild-2017-313697.
15. F. J. Walther, A. L. Den Ouden, and S. P. Verloove-Vanhorick, “Looking back in time: Outcome of a national cohort of very preterm infants born in The Netherlands in 1983,” *Early Hum. Dev.*, vol. 59, no. 3, pp. 175–191, 2000, doi: 10.1016/S0378-3782(00)00094-3.
16. Health Council of the Netherlands, “Intensive care for newborn infants,” The Hague, 1991.
17. Health Council of the Netherlands, “Intensive care at birth,” The Hague, 2000.
18. H. E. McHaffie *et al.*, “Withholding/withdrawing treatment from neonates: Legislation and official guidelines across Europe,” *J. Med. Ethics*, vol. 25, no. 6, pp. 440–446, 1999, doi: 10.1136/jme.25.6.440.
19. S. P. Verloove-Vanhorick, “Management of the neonate at the limits of viability: The Dutch viewpoint,” *BJOG An Int. J. Obstet. Gynaecol.*, vol. 113, no. SUPPL. 3, pp. 13–16, 2006, doi: 10.1111/j.1471-0528.2006.01119.x.
20. E. von Elm, D. G. Altman, M. Egger, S. J. Pocock, P. C. Gøtzsche, and J. P. Vandenbroucke, “The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies,” *Int. J. Surg.*, vol. 12, no. 12, pp. 1495–1499, 2014, doi: 10.1016/j.ijsu.2014.07.013.
21. K. M. van der Pal-de Bruin, S. M. van der Pal, S. P. Verloove-Vanhorick, and F. J. Walther, “Profiling the preterm or VLBW born adolescent; implications of the Dutch POPS cohort follow-up studies,” *Early Hum.*

Dev., vol. 91, no. 2, pp. 97–102, 2015, doi: 10.1016/j.earlhumdev.2014.12.007.

22. J. M. Kerstjens, A. F. De Winter, I. F. Bocca-Tjeertes, E. M. J. Ten Vergert, S. A. Reijneveld, and A. F. Bos, "Developmental delay in moderately preterm-born children at school entry," *J. Pediatr.*, vol. 159, no. 1, pp. 92–98, 2011, doi: 10.1016/j.jpeds.2010.12.041.
23. I. F. A. Bocca-Tjeertes, S. Van Buuren, A. F. Bos, J. M. Kerstjens, E. M. Ten Vergert, and S. A. Reijneveld, "Growth of preterm and full-term children aged 0-4 years: Integrating median growth and variability in growth charts," *J. Pediatr.*, vol. 161, no. 3, pp. 460-465.e1, 2012, doi: 10.1016/j.jpeds.2012.03.016.
24. RECAP_WP3, "Harmonisation Guidelines Compiled by ULEIC," 2020.
25. D. Doiron *et al.*, "Data harmonization and federated analysis of population-based studies: The BioSHaRE project," *Emerg. Themes Epidemiol.*, vol. 10, no. 1, pp. 22–24, 2013, doi: 10.1186/1742-7622-10-12.
26. I. Fortier *et al.*, "Maelstrom Research guidelines for rigorous retrospective data harmonization," *Int. J. Epidemiol.*, vol. 46, no. 1, pp. 103–115, 2017, doi: 10.1093/ije/dyw075.
27. H. C. Lee, M. V Bennett, J. Schulman, J. B. Gould, and J. Profit, "Estimating Length of Stay by Patient Type in the Neonatal Intensive Care Unit," *Am J Perinatol*, vol. 33, no. 08, pp. 751–757, 2016.
28. G. M. S. J. Stoelhorst, "Changes in Neonatology: Comparison of Two Cohorts of Very Preterm Infants (Gestational Age <32 Weeks): The Project on Preterm and Small for Gestational Age Infants 1983 and The Leiden Follow-Up Project on Prematurity 1996-1997," *Pediatrics*, vol. 115, no. 2, pp. 396–405, 2005, doi: 10.1542/peds.2004-1497.
29. M. J. K. De Kleine *et al.*, "Lower mortality but higher neonatal morbidity over a decade in very preterm infants," *Paediatr. Perinat. Epidemiol.*, vol. 21, no. 1, pp. 15–25, 2007, doi: 10.1111/j.1365-3016.2007.00780.x.
30. S. Anthony, L. Den Ouden, R. Brand, P. Verloove-Vanhorick, and J. B. Gravenhorst, "Changes in perinatal care and survival in very preterm and extremely preterm infants in the Netherlands between 1983 and 1995," *Eur. J. Obstet. Gynecol. Reprod. Biol.*, vol. 112, no. 2, pp. 170–177, 2004, doi: 10.1016/S0301-2115(03)00328-2.
31. S. J. Oddie, L. Young, and W. Mcguire, "Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants," *Cochrane Database Syst. Rev.*, vol. 2017, no. 8, 2017, doi: 10.1002/14651858.CD001241.pub7.
32. J. Morgan, L. Young, and W. Mcguire, "Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants," *Cochrane Database Syst. Rev.*, vol. 2014, no. 12, 2014, doi: 10.1002/14651858.CD001970.pub5.
33. J. P. Foster, M. J. Cole, and R. Seth, "Oral immunoglobulin for preventing necrotizing enterocolitis in preterm and low birth weight neonates," *Cochrane Database Syst. Rev.*, vol. 2016, no. 4, 2016, doi: 10.1002/14651858.CD001816.pub3.
34. J. L. Y. Cheong *et al.*, "Head Growth in Preterm Infants : Correlation With," *Pediatrics*, vol. 121, no. 6, pp. 1534–40, 2008, doi: 10.1542/peds.2007-2671.
35. A. Sansavini, A. Guarini, R. Alessandroni, and G. Fardella, "The effect of gestational age on developmental outcomes : a longitudinal study in the first 2 years of life," *Child. Care. Health Dev.*, pp. 26–36, 2010, doi: 10.1111/j.1365-2214.2010.01143.x.

36. O. Picciolini *et al.*, “Neurodevelopmental outcome of extremely low birth weight infants at 24 months corrected age : a comparison between Griffiths and Bayley Scales,” *BMC Pediatr.*, pp. 1–9, 2015, doi: 10.1186/s12887-015-0457-x.
37. V. Brévaut-Malaty, M. Busuttil, M. A. Einaudi, A. S. Monnier, C. D’Ercole, and C. Gire, “Longitudinal follow-up of a cohort of 350 singleton infants born at less than 32 weeks of amenorrhea: neurocognitive screening, academic outcome, and perinatal factors,” *Eur. J. Obstet. Gynecol. Reprod. Biol.*, vol. 150, no. 1, pp. 13–18, 2010, doi: 10.1016/j.ejogrb.2010.01.001.
38. J. Zeitlin *et al.*, “Use of evidence based practices to improve survival without severe morbidity for very preterm infants: Results from the EPICE population based cohort,” *BMJ*, vol. 354, pp. 1–10, 2016, doi: 10.1136/bmj.i2976.
39. American Academic of Pediatrics, “Postnatal Corticosteroids to Treat or Prevent Chronic Lung Disease in Preterm Infants,” *Pediatrics*, vol. 109, no. 2, pp. 330–338, 2002.
40. OECD, “Health risks - daily smokers,” *https://data.oecd.org/healthrisk/daily-smokers.htm*, 2010. .
41. OECD, “Fertility rates (indicator),” *https://data.oecd.org/pop/fertility-rates.htm*, 2021. .
42. OECD, “Caesarean sections (indicator),” *https://data.oecd.org/healthcare/caesarean-sections.htm*, 2021. .
43. L. Schmidt, T. Sobotka, J. G. Bentzen, and A. N. Andersen, “Demographic and medical consequences of the postponement of parenthood,” *Hum. Reprod. Update*, vol. 18, no. 1, pp. 29–43, 2012, doi: 10.1093/humupd/dmr040.
44. OECD, “SF2.3: Age of mothers at childbirth and age-specific fertility This1 Updated: 29-05-2019,” *http://www.oecd.org/els/soc/SF_2_3_Age_mothers_childbirth.pdf*, 2019. .
45. T. Bianco-Miotto, J. M. Craig, Y. P. Gasser, S. J. Van Dijk, and S. E. Ozanne, “Epigenetics and DOHaD: From basics to birth and beyond,” in *Journal of Developmental Origins of Health and Disease*, Oct. 2017, vol. 8, no. 5, pp. 513–519, doi: 10.1017/S2040174417000733.
46. E. Kajantie *et al.*, “Common Core Assessments in follow-up studies of adults born preterm—Recommendation of the Adults Born Preterm International Collaboration,” *Paediatr. Perinat. Epidemiol.*, no. May, pp. 1–17, 2020, doi: 10.1111/ppe.12694.
47. J. Zeitlin *et al.*, “Priorities for collaborative research using very preterm birth cohorts,” *Arch. Dis. Child. Fetal Neonatal Ed.*, vol. 105, no. 5, pp. 538–544, 2020, doi: 10.1136/archdischild-2019-317991.

Figures

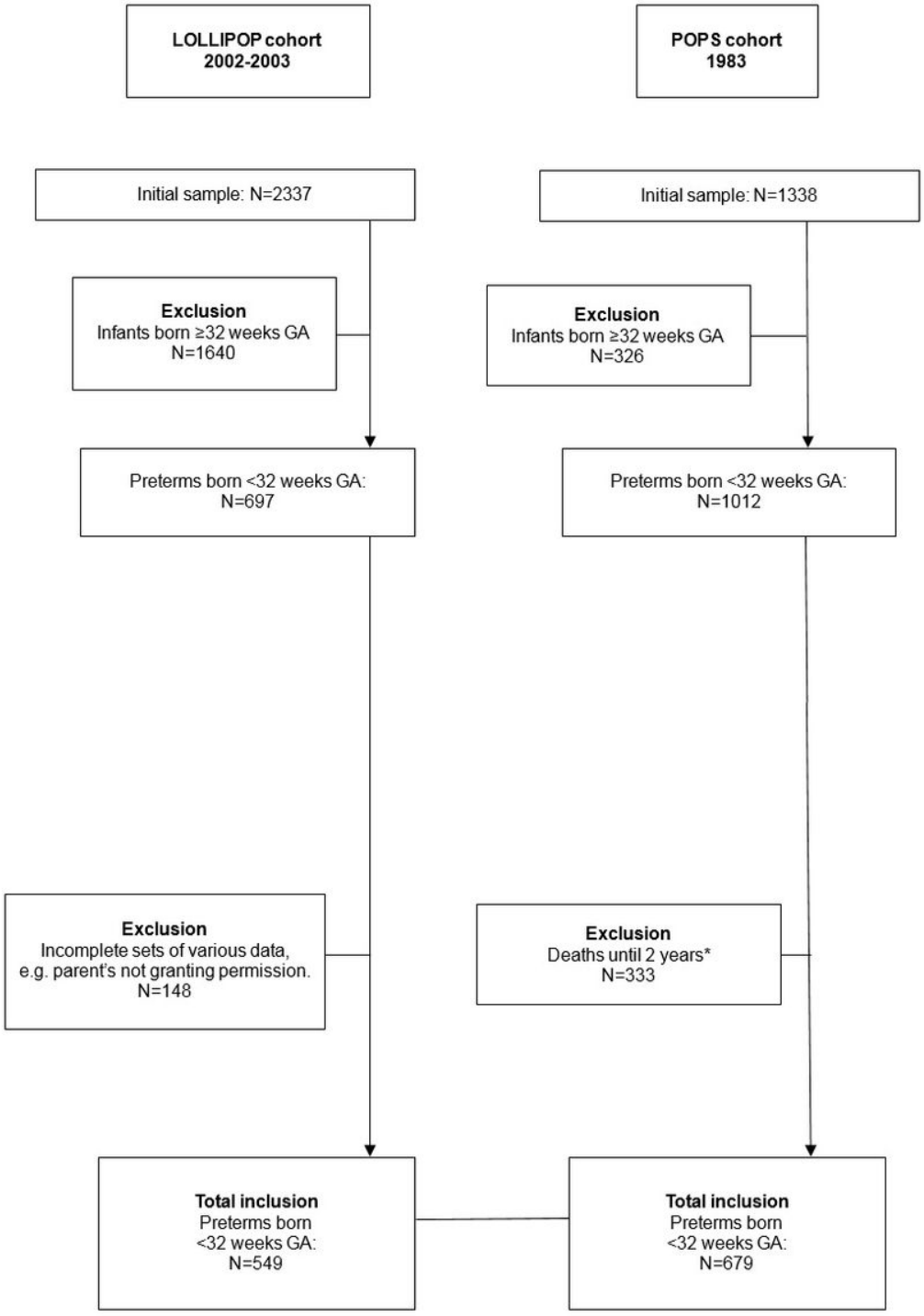

Figure 1

Flowchart of participant selection from the original POPS and LOLLIPOP cohorts * All cases with severe congenital malformations died before 2 years of age.

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