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ORIGINAL ARTICLE

Health-related quality of life in two birth cohorts of extremely preterm born adults

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Abstract

Aim: Investigate potential long-term cohort influences on health-related quality of life (HRQoL) in adults born extremely preterm (EP) during the 1980–90s, in view of advancements in neonatal care within that timeframe.

Methods: Two cohorts of EP-born adults (82–85 cohort and 91–92 cohort) enrolling matched term controls, were compared. Participants were assessed at 18 years and again in their mid-twenties using the Child Health Questionnaire Children Form-87 (CHQ-CF87) and the Short Form Health Survey (SF-36).

Results: At 18 years, 77 (90%) EP-born and 75 (93%) term controls had data, followed by 67 (78%) EP-born and 66 (82%) term controls in their mid-twenties. At 18 years, there were no differences across the birth decades, and EP-born and term-born reported relatively similar HRQoL scores. In the mid-twenties, birth decade did also not significantly impact HRQoL scores, although the EP-born 82–85 cohort scored numerically poorer than the 91–92 cohort in three domains. Term controls scored similarly across birth decade in all domains. Regarding influence from neonatal factors, postnatal corticosteroids had a negative impact in some domains.

Conclusion: No significant differences in HRQoL were observed between EP-born adults from the 82–85 cohort versus the 91–92 cohort, although the EP-born 82–85 cohort tended to score poorer in their mid-twenties.

KEYWORDS
extremely preterm, long-term outcome, preterm adults, quality of life, self-rated health, SF-36

1 | INTRODUCTION

Perinatal medicine underwent substantial advancements in the late 1980s and early 1990s, leading to remarkable improvements in the survival of premature infants, particularly those born extremely preterm (EP), defined by birth below 28 weeks gestational age (GA).[1] The introduction of surfactant played a key role in this development,[2] as did increased use of corticosteroids before and after birth, better respiratory support, better nursing practices, a range of technological advancements as well as a

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; CHQ-CF87, Child Health Questionnaire Child Form-87; CI, confidence intervals; CP, cerebral palsy; EP, extremely preterm; GA, gestational age; HRQoL, Health-related quality of life; SF-36, Short Form Health Survey; VP, very preterm; VLBW, very low birth weight.

more structured handling that influenced nearly all aspects of our neonatal intensive care units (NICUs).[3] These transformative changes brought substantial benefits to all infants born preterm, but particularly influenced survival of those born at the limit of viability. Thus, reflecting on the past, the decade of birth determined the treatment options available to these infants as well as their likelihood of survival, and probably also their subsequent morbidity in later life.[4] Long-term overall cohort effects of these advancements remain inadequately characterised. One could expect improved long-term outcomes as enhanced care benefits all preterm-born, or poorer outcomes due to survival of more high-risk individuals. Recent studies on premature infants have indicated a rising number facing severe neonatal morbidities, which is likely to influence also their long-term outcomes.[5,6] However, we have a very limited understanding of such trends in adults, and the evidence is partly conflicting, probably because high survival rates are relatively recent achievements, allowing for few studies, usually with few participants.

Health-related quality of life (HRQoL) is a crucial measure of human well-being, encompassing assessments of domains related to physical, mental, emotional, and social functioning.[7] Besides health and illness, HRQoL is influenced also by socioeconomic factors and gender, where females seem to report lower HRQoL in the general population.[8] A systematic review of adults born very preterm (VP) or with very low birth weight (VLBW), aged between 18 and 36 years, found no evidence of reduced HRQoL in preterm compared to term-born groups, but split by gender it seems that VP or VLBW females are at increased risk of poorer HRQoL.[9]

Moreover, a meta-analysis of health utilities reported lower values across preterm study groups, spanning from childhood to adulthood. Only preterm adults born before 1987 were included.[10] Previous publications from our cohorts have revealed inferior HRQoL in adults born EP in 1982–85 compared to term-born controls, both at 24 and 34 years of age.[11,12] However, no differences in HRQoL were observed between adults born EP in 1991–92 and term-born controls when assessed at 27 years of age.[13] Notably, we have not found studies comparing HRQoL in similarly aged adults born EP during different time epochs.

The association between neonatal factors and HRQoL outcomes has been poorly investigated. Bronchopulmonary dysplasia (BPD) and intraventricular haemorrhage (IVH) were associated with poorer physical health in early adulthood in a Swedish VLBW cohort.[14] A recent article by Kim et al.[15] reported lower HRQoL in very preterm children with BPD and severe non-respiratory morbidity. Moreover, EP-born children from our 91–92 cohort, who received neonatal steroids scored lower in the domain for role/social functioning at 10 years of age.[16] Some studies have found that low maternal education affected negatively mental, intellectual, and HRQoL issues for EP-born.[17,18]

Building on our previously reported findings from these two cohorts, representing individuals born in different epochs characterised by transformative changes in neonatal intensive care (1980s vs. 1990s), we wanted to investigate potential long-term cohort effects on HRQoL outcomes at two different assessment points in adulthood. Thus, the aim of this study was to investigate cohort differences in HRQoL by comparing early adulthood HRQoL between two birth cohorts (1982–85 vs. 1991–92), with assessments performed at 18 years and in the mid-twenties. Matched term-controls were included to illustrate possible changes in HRQoL during this epoch which were caused by societal changes but unrelated to preterm birth.

Key Notes

- Transformative changes occurred in perinatal medicine during the 1980s and 1990s; however, the implications for the later health-related quality of life (HRQoL) in adults born extremely preterm (EP) remain unknown.
- Birth epoch did not significantly influence self-reported HRQoL in EP-born, measured twice during early adulthood.
- In the mid-twenties, the 1980s cohort showed non-significant HRQoL reductions compared to the 1990s, hinting a possible improvement over time.

2 | METHODS

2.1 | Study design, participants and setting

This study includes data from two population-based cohorts of individuals born EP (defined by GA ≤28 weeks or birth weight (BW) ≤1000 g) within a defined area in Norway during 1982–85 (82–85 cohort) and 1991–92 (91–92 cohort). The participants were identified from the admission protocols of the only regional NICU at Haukeland University Hospital. Substantial improvements in the NICU had occurred by the time the 91–92 cohort was born. Exogenous surfactant (Exosurf) was available, administered as prescribed in the Osiris trail.[19] More advanced Infant Star ventilators (*Infrasonics*, *San Diego*, *USA*) were in place, as was pulse oximetry which allowed for better monitoring of ventilatory support and oxygen therapy.[20] With modern cannulas, continuous radial arterial blood pressure surveillance had become routine, and adequate intravenous nutrition was facilitated by peripheral central venous catheters. The importance of standardisation of complex neonatal intensive care schemes, education and quality control was advocated internationally through the Vermont Oxford Network, established in 1989.[21] At our department, a manual with guidelines for all aspects of intensive care was developed in the late 1980s, ensuring a systematic approach to all decisions, interventions, and nursing practices.

For both cohorts, individually matched term-born controls were identified and recruited, as previously described.[11,22] Assessments were performed twice; at age 18 in both cohorts and thereafter in the mid-twenties, with mean age of 24 for the 82–85 cohort and mean age of 27 for the 91–92 cohort (hereafter referred to as mid-twenties).

Standardised questionnaires (presented below) were predominantly completed by participants during their physical follow-up sessions; however, a few chose to complete them at home and returned them by mail. Results from the follow-ups for each birth cohort have previously been published separately.[11,22]

2.2 | Measures

2.2.1 | Clinical and socio-demographic data

Perinatal characteristics of the EP-born subjects were obtained from medical records. Subsequent clinical data were gathered through a combination of participant self-reports, clinical examinations conducted by a paediatrician during follow-up sessions, and further reference to medical records. GA was determined by the mothers' last menstruation in the 82–85 cohort, and by ultrasound scans at 17–18 weeks gestation for the 91–92 cohort. Bronchopulmonary dysplasia (BPD) was defined as supplemental oxygen or respiratory support at postmenstrual age ≥36 weeks. Major disability was defined as disabling CP, functional blindness, or deafness according to WHO. Socio-demographic data were obtained with validated questionnaires used in population studies in Norway (http://www.hunt.ntnu.no). Data on maternal education were collected at the 10-year assessment and dichotomised with higher education defined as 3 year or more of college education.

2.2.2 | Child health questionnaire child Form-87 (CHQ-CF87)

Self-reported HRQoL at 18 years was measured in both birth cohorts by using the CHQ-CF87 questionnaire, a generic instrument designed to measure functional health and well-being of subjects 10–18 years of age.[23] The CHQ-CF87 captures domains of HRQoL with 12 subscales of 87 items: physical functioning (nine items), role emotional (three items), role behavioural (three items), role-physical (three items), bodily pain (two items), behaviour (17 items), mental health (16 items), self-esteem (14 items), general health (12 items), family activities (six items) and family cohesion (one item). And one last item 'change in health', not used in this study. Each item has 4–6 ordered response levels, such as 'very often' to 'not at all', with corresponding numerical scores. The item scores for each scale are summarised and transformed into a sum score ranging from 0 (poor) to 100 (optimal). A validated Norwegian version of the questionnaire was used.[24]

2.2.3 | Short Form 36-Item Health Survey (SF-36)

Self-reported HRQoL in the mid-twenties was measured by using the Short Form Health Survey (SF-36) version 1.1 questionnaire in the 82–85 cohort and RAND-36 in the 91–92 cohort. Due to changes in the licensing agreement, we replaced SF-36 with RAND-36 (Norwegian version 1) at the last follow-up in 2017. This RAND-36 version is equivalent to the 36-item SF-36 version 1.1, but employs more modern language in the Norwegian translation. We used the SF-36 scoring procedure. SF-36 is a generic measure assessing self-perceived functional health and well-being through eight health domains: physical functioning (10 items), role-physical (four items), role-emotional (three items), bodily pain (two items), general health (five items), vitality (four items), social functioning (two items) and mental health (five items). Except for the two role-functioning scales, the items have 3–6 point ordered response levels, with the preceding 4 weeks as the recall period, except for physical functioning and general health, which pertain to the current status. The raw scores for each SF-36 sub scales were based on the mean of valid items if at least half of the items in each scale were valid, and then linearly transformed into a scale from 0 to 100, with higher scores indicating better functional health and well-being.[25,26] The questionnaire has demonstrated good reliability and validity,[25] Norwegian populations included.[8] Term-born participants were expected to represent the general population and the results from the questionnaire were in line with normative data of the Norwegian population.[8]

2.3 | Statistical analysis

Descriptive data were reported as means, standard deviations, counts and percentages, as appropriate. We used Welch's *t*-test and Fisher Exact test to compare outcomes variables between the two cohorts (Table 1). A *p*-value less than 0.05 is characterised as statistically significant, and 95% confidence intervals (CI) are reported where relevant. SPSS statistical package version 26 was used for all descriptive data.

There were some missing responses for the mid-twenties' follow-up (SF-36), and we used multiple imputation to improve accuracy and statistical power for analyses involving these scores (Tables 2 and 3).[27] The data were imputed using 'mice()' function from the R package 'mice' version 3.14.0, with 30 imputations, 50 iterations, and otherwise default arguments. All analyses using imputed data were performed using R version 4.2.1. The 'mi.t.test()' function from the 'MKmisc' package version 1.8 was used to conduct Welch's t-tests on imputed data, with separate analyses for EP-born and term-born participants. In the imputation model, we included variables deemed as potential predictors of missing values or the probability of a variable having missing values, namely age, sex, cohort, the HRQoL scores, use of postnatal steroids and

TABLE 1 Clinical characteristics and demographics for EP and term-born subjects.

	Era of birth		
	82–85 cohort	91–92 cohort	*p*-Value
Characteristics at 18 years			
EP-born, participated/eligible, *n*	46/51	31/35	
Term-born, participated/eligible, *n*	46/46	29/35	
Birth weight in grams			
EP-born, mean (SD)	1014 (193)	942 (209)	0.13
Term-born, mean (SD)	3441 (311)	3574 (286)	0.06
Characteristics data of the EP-born subjects			
Gestational age in weeks, mean (SD)	27.3 (1.4)	26.8 (1.8)	0.21
Ventilator days, mean (SD)	11 (12)	9 (12)	0.38
Postnatal days with oxygen treatment, mean (SD)	49 (40)	60 (50)	0.28
Antenatal steroids, *n* (%)	15 (33)	12 (40)	0.63
Surfactant, *n* (%)	0 (0)	15 (48)	**<0.001**
Postnatal steroids, *n* (%)	4 (9)	9 (29)	**0.031**
BPD, *n* (%)	12 (26)	12 (39)	0.32
Maternal infection, *n* (%)	8 (18)	11 (36)	0.11
Higher maternal education,[a] *n* (%)	32 (36)	19 (32)	0.72
Disabling Cerebral Palsy, *n* (%)	4 (8)	0 (0)	0.13
Blind, *n* (%)	3 (7)	0 (0)	0.27
Deaf, *n* (%)	2 (4)	0 (0)	0.51
Characteristics at mid-twenties			
EP- born, participated/eligible, *n*	43/51	24/35	
Term-born, participated/eligible, *n*	40/46	26/35	
Age EP-born, (SD)	24.2 (1.3)	26.6 (0.6)	**<0.001**
Age Term-born, (SD)	24.7 (1.3)	26.6 (0.6)	**<0.001**
Gender, male/female EP, *n*	25/21	13/18	
Gender, male/female term-born, *n*	25/21	9/20	

Note: The bolded values are statistically significant ($p < 0.05$). Cohort differences were tested using Welch's *t*-test for continuous variables and Fisher's Exact test for categorical variables.

Abbreviations: BPD, bronchopulmonary dysplasia; EP, extremely preterm;

[a]Maternal education at least 3 years college education or a university degree.

maternal education. The number of missing data are provided in Table S3.

To examine other predictors of the outcome variables, we also fitted multiple regression models with cohort, postnatal steroid administration, gender and maternal education as predictors.

2.4 | Ethics

The study protocol was approved by the Regional Committee for Medical Research Ethics for Western Norway (Protocol no. 17920 and 2017/628), and the study was performed in accordance with the Helsinki Declaration. All participants or their guardians gave informed written consent.

3 | RESULTS

3.1 | Subjects

At 18 years, 77 (90%) EP-born participated, whereas 67 (78%) participated in their mid-twenties. Regarding term-born controls, 75 (93%) participated at 18 years and 66 (82%) in their mid-twenties (Figure 1).

3.2 | Perinatal characteristics between the two cohorts

Participants' characteristics for each cohort are summarised in Table 1. Birth weight (BW), gestational age, days on ventilator,

TABLE 2 Self-reported HRQoL at 18 years of age in subjects born EP or on term, comparing two periods (82–85 vs. 91–92).

	EP-born					Term-born				
	82–85	91–92	Difference			82–85	91–92	Difference		
	Mean (SD)	Mean (SD)	Est.	95% CI	*p*-Value	Mean (SD)	Mean (SD)	Est.	95% CI	*p*-Value
CHQ-CF87[a]										
Physical function	86.5 (25.3)	93.8 (12.7)	7.3	−1.0 to 15.7	0.08	95.1 (7.7)	98.1 (6.9)	3.0	−0.3 to 6.3	0.07
Role emotional	86.0 (25.6)	87.4 (24.5)	1.5	−9.6 to 12.5	0.79	94.0 (13.8)	92.7 (17.8)	−1.3	−8.6 to 6.0	0.73
Role behavioural	97.2 (7.9)	95.4 (15.0)	−1.8	−7.4 to 3.8	0.52	98.6 (6.9)	99.0 (4.9)	0.5	−2.2 to 3.1	0.72
Role physical	93.2 (17.5)	94.6 (16.4)	1.5	−6.0 to 8.9	0.70	96.1 (10.8)	99.6 (5.9)	3.4	−0.4 to 7.2	0.08
Bodily pain	72.3 (29.1)	73.1 (25.9)	0.8	−11.2 to 12.7	0.90	73.0 (25.5)	76.0 (24.1)	3.0	−8.1 to 14.1	0.59
Behaviour	79.1 (12.5)	75.9 (16.6)	−3.1	−9.8 to 3.5	0.35	79.6 (11.3)	78.0 (11.8)	−1.5	−6.7 to 3.7	0.56
Mental health	75.0 (15.7)	72.4 (17.9)	−2.7	−10.2 to 4.9	0.48	75.6 (12.6)	74.8 (13.4)	−0.8	−6.7 to 5.1	0.78
Self-esteem	70.7 (15.2)	69.5 (16.5)	−1.2	−8.2 to 5.8	0.73	70.6 (12.3)	75.0 (15.8)	4.4	−2.1 to 10.8	0.18
General health	66.8 (18.4)	70.1 (18.8)	3.3	−4.9 to 11.6	0.42	66.7 (17.7)	72.8 (18.3)	6.1	−2.0 to 14.2	0.14
Family activities	86.5 (15.4)	87.5 (19.2)	1.0	−6.8 to 8.8	0.81	88.0 (18.1)	90.9 (15.4)	2.9	−4.5 to 10.4	0.43
Family cohesion item	68.7 (27.6)	73.2 (28.9)	4.5	−8.1 to 17.0	0.48	74.7 (24.7)	74.6 (28.2)	−0.1	−12.1 to 11.9	0.99

Note: Analyses performed with Welch's *t*-tests on multiply imputed data.

Abbreviations: CI, confidence interval; EP, Extremely Preterm; HRQoL, health-related quality of life.

[a]Child Health Questionnaire Child Form-87 (CHQ-CF87) with possible domains scorers from 0 to 100, where higher scores indicate better functional health and well-being.

TABLE 3 Self-reported HRQoL of adults in their mid-twenties born EP or on term, comparing two periods (82–85 vs. 91–92).

	EP-born					Term-born				
	82–85	91–92	Difference			82–85	91–92	Difference		
	Mean (SD)	Mean (SD)	Est.	95% CI	*p*-Value	Mean (SD)	Mean (SD)	Est.	95% CI	*p*-Value
SF-36[a]										
Physical Function	86.4 (25.4)	92.7 (13.7)	6.3	−2.4 to 15.0	0.16	93.7 (13.6)	97.0 (9.3)	3.3	−1.6 to 8.1	0.18
Role Physical	79.1 (31.9)	83.9 (33.6)	4.8	−9.6 to 19.2	0.50	85.2 (30.1)	89.5 (24.8)	4.4	−7.8 to 16.5	0.48
Bodily Pain	70.1 (26.5)	75.4 (26.2)	5.3	−6.2 to 16.9	0.36	79.6 (24.7)	82.3 (23.4)	2.7	−7.7 to 13.1	0.61
General Health	73.6 (24.8)	69.6 (27.6)	−4.0	−15.5 to 7.6	0.49	76.2 (22.2)	75.3 (23.8)	−0.9	−11.6 to 9.8	0.87
Vitality	52.2 (20.3)	59.1 (23.5)	6.9	−2.9 to 16.7	0.16	59.3 (16.1)	63.2 (21.4)	3.9	−4.7 to 12.6	0.36
Social Function	78.3 (28.3)	79.3 (31.1)	0.9	−12.2 to 14.1	0.89	88.6 (20.1)	87.0 (24.2)	−1.6	−11.7 to 8.4	0.75
Role Emotional	67.8 (42.1)	79.2 (40.2)	11.4	−6.6 to 29.4	0.21	86.6 (34.4)	85.8 (35.7)	−0.8	−16.6 to 15.1	0.92
Mental Health	71.7 (17.6)	74.1 (19.2)	2.4	−6.0 to 10.8	0.57	79.7 (13.2)	78.7 (19.5)	−1.0	−8.6 to 6.6	0.79

Note: Analyses performed with Welch's *t*-tests on multiply imputed data.

Abbreviations: CI, confidence interval; EP Extremely Preterm; HRQoL, health-related quality of life.

[a]Short Form Health Survey (SF-36), with possible domains scorers from 0 to 100, where higher scores indicate better functional health and well-being.

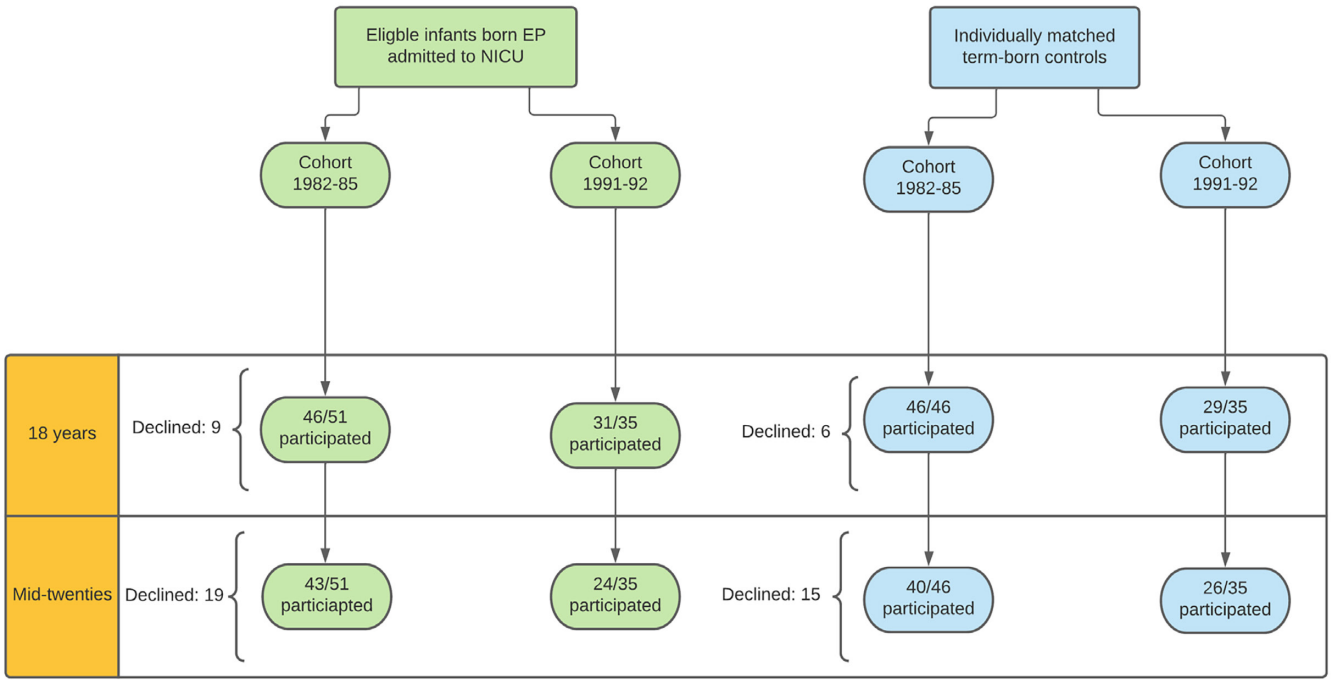

FIGURE 1 Flow chart of the extremely preterm (EP) born subjects and matched term-born controls from the two cohorts at the follow-up points.

postnatal days with oxygen, antenatal steroids were similar across the two cohorts. Surfactant was unavailable for the 82–85 cohort and prescribed to 48% of the participants of the 91–92 cohort. Postnatal steroids were prescribed to significantly more EP-born in the 91–92 cohort. Major disability (defined as CP, blind or deaf) was found among participants in the 82–85 cohort, but not in the 91–92 cohort. For the term-born participants, mean BW was similar in both cohorts.

3.3 | Comparison of self-reported HRQoL between the two birth-cohorts at age 18

At 18 years of age, we were unable to show statically significant differences between the cohorts born EP during 1982–85 versus 1991–92 regarding the HRQoL outcomes. EP-born and term-born reported relatively similar scores in all domains, and there were no differences across decade of birth (Table 2 and Figure 2).

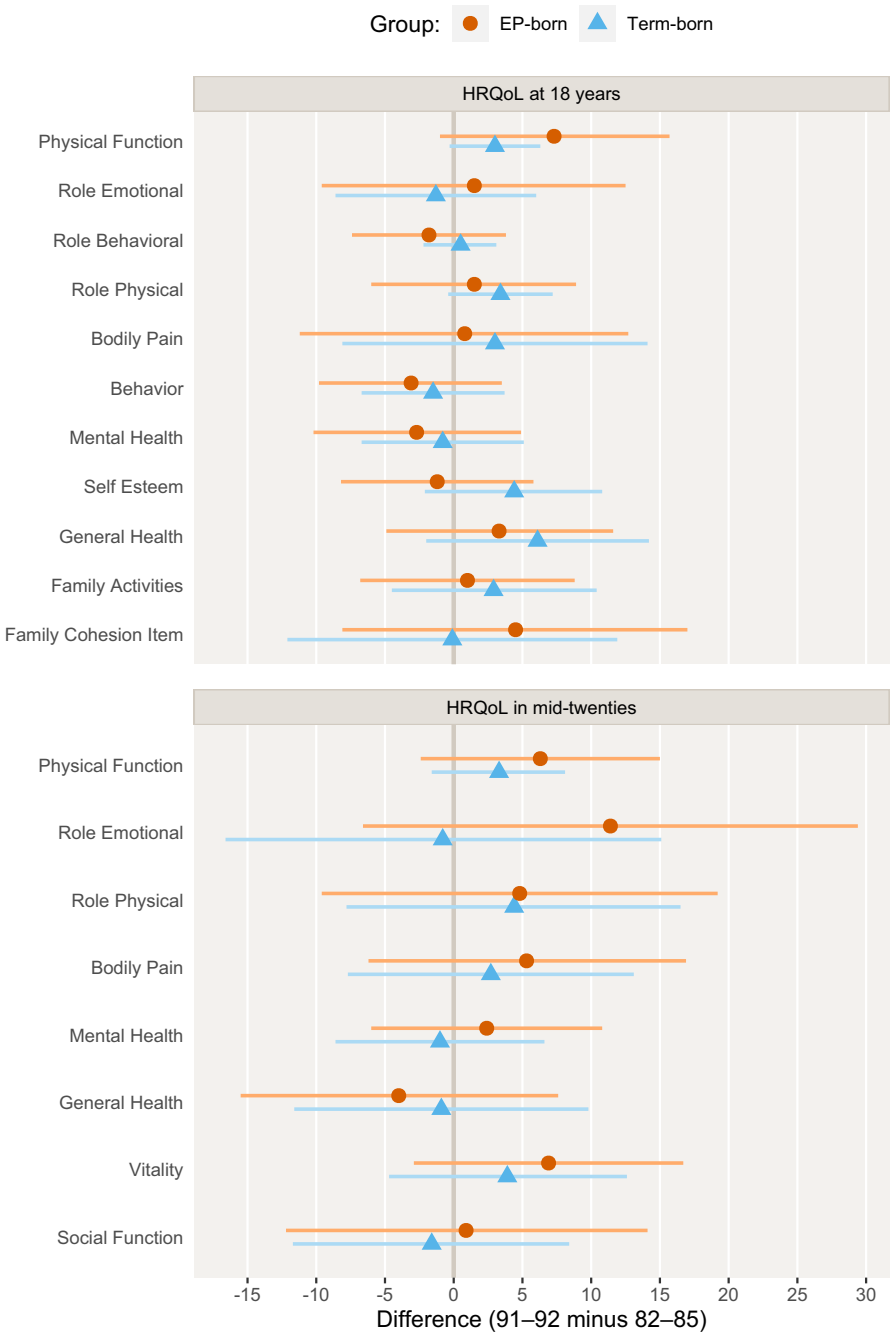

FIGURE 2 Mean differences and confidence intervals of self-reported HRQoL domains between the two cohorts of adults born extremely preterm (EP) and term-born controls. Analyses performed with regression analysis on multiply imputed data.

Regression models showed that EP-born who had been treated with postnatal steroids scored significantly lower in role physical, self-esteem and mental health (mean difference −16.5, −10.6 and −9.7, respectively) (Table S1). EP-born females scored significantly lower in the domains role emotion, mental health, self-esteem, bodily pain and role physical compared to EP-born males (mean difference −18.9, −14.1, −12.3, −19.0 and −7.7, respectively) (Table S1). Among the EP participants, higher maternal education was associated with higher scores in role emotion and role physical (Table S1).

3.4 | Comparison of self-reported HRQoL between the two birth cohorts in their mid-twenties

In their mid-twenties, we were also unable to show statically significant differences between the cohorts born EP during 1982–85 versus 1991–92 regarding HRQoL outcomes. The EP-born participants from the 82–85 cohort scored numerically lower in most domains when compared to the 91–92 cohort (Table 3). The largest estimated mean differences between the birth cohorts were observed in the domains of physical functioning, vitality and role emotional. The

confidence intervals were wide, as visualised in Figure 2. The term-born participants scored relatively similarly across the two birth cohorts, and the confidence intervals were generally narrower, except for role emotion and role physical.

Regression models showed that the EP-born who had been treated with postnatal steroids continued to score significantly lower in their mid-twenties in the domains of social functioning and general health (mean difference −21.9 and −17.0, respectively) when compared to EP-born who had not been treated with postnatal steroids (Table S2). Additionally, female EP-born scored significantly lower in the domains of bodily pain (mean difference −13.1) compared to EP-born males (Table S2), there was no effect of maternal education on HRQoL outcomes in the EP-participants (Table S2).

4 | DISCUSSION

This study compared HRQoL in adults born EP in two different birth cohorts (1982–85 versus 1991–92), a period characterised by transformative changes in our NICUs. The findings indicate that self-reported HRQoL was not significantly influenced by the decade of birth, nor by 18 years of age, nor by their mid-twenties. Thus, despite vast advancements in medical care and technology and survival rates, we could not establish an overarching significant impact on HRQoL in early adulthood. However, as those born EP in the early 1980s reached their mid-twenties, there were non-significant trends of lower mean scores in most domains, compared to those born EP in the 1990s. This may hint at positive long-term effects relating to the developments that occurred during the 1980–90s. Notably, term-born controls scored similarly across these same birth epochs, suggesting that the findings in the EP groups are tied to prematurity and not societal confounders. Regarding neonatal predictors, treatment with postnatal steroids was significantly associated with poorer role physical, self-esteem and mental health at 18 years, followed by diminished social function and general health outcomes in the mid-twenties. However, there is a high risk of 'bias by indication' being at play here, given that this treatment is typically administered to infants who are generally more severely ill than average.

Although no significant differences were observed between the two birth-cohorts, when the participants had reached their mid-twenties, there was a relatively consistent tendency for poorer scores in the cohort born 1982–1985 compared to those born 1991–92 regarding the domains physical functioning, vitality, and role emotional. These domains concern elements of high everyday importance, such as the ability to walk, dress themselves, feelings of tiredness and experiencing problems at work due to emotional issues. Looking at the individual figures, some EP-born participants from the 82–85 cohort scored extraordinary poorly, whereas the majority of EP-born in the 91–92 cohort scored closer to the ceiling. We may speculate that this tendency could be attributed to the advancements in medical care that took place between these two decades, coupled with higher prevalence of severe major disabilities in the 82–85 cohort compared to no sequelae of this kind in the 91–92 cohort.[12] It is of interest that other somatic traits had also improved over this time-span, such as lung function.[4]

Contrary to our findings, two recent studies focusing on children born in the post-surfactant era have reported a decline in parental-reported HRQoL ratings in the most recently born groups. This was observed when comparing children born EP in 1991–1992 versus in 1997 and 2005, as well as when comparing cohorts from 1995 to 2006.[17,28] These studies had enrolled participants born at a mean GA of 25 weeks: i.e. considerably more immature than our groups, which certainly may contribute to the explanatory context. Presently, infants born as early as 22 weeks GA are being resuscitated in some countries, with survival rates between 22 and 24 weeks varying from 10% to approximately 50%, increasing with higher GA.[5] A recent Swedish study found that the majority of children born between GA 22–24 weeks displayed neurodevelopmental disorders during follow-up from ages 2–13 years.[29] We cannot predict how their HRQoL will develop into adulthood since none of these individuals have reached that age. This emphasises the need for further investigations and continuous monitoring of this group.

As indicated by the confidence intervals of most parameters, outcomes varied substantially between the individuals. Thus, factors associated with poor outcomes are important to define. In our study, BPD was a common neonatal morbidity. A study of EP-born children from 11 European countries revealed that HRQoL was particularly impaired both by BPD as well as by other severe non-respiratory morbidities.[15] We also observed a correlation between poorer HRQoL and the administration of postnatal steroids. However, it is important to bear in mind that neonates treated with postnatal steroids constitute a particularly vulnerable group who require steroids to facilitate weaning from ventilatory support, and therefore are at heightened risk of adverse outcomes, that is bias by indication is probably at play here.

The similar HRQoL outcomes between the two birth cohorts suggest that changes in neonatal care from 1982–1985 to 1991–1992 were less impactful than expected. This is despite advancements like improved ventilators, introduction of pulse oximetry, and modern cannulas, which reduced harm to neonates.[20] The 91–92 cohort benefited from non-invasive oximetry, enhancing therapy accuracy and reducing infant disturbances. Moreover, new guidelines for systematic management marked a distinct shift in care practices.

We could not find associations between maternal education and HRQoL in their twenties, contrasting some but in line with others.[15,30] Having a mother with education <10 years in the Nordic countries is associated with a higher risk of very or moderately preterm birth.[31] However, the welfare system in the Nordic countries is unique and may impact the significance of sociodemographic factors, such as the mothers' education.

In summary, minor differences were observed between the birth cohorts, with a possible trend towards better outcomes in the 1991–1992 cohort. The role of postnatal steroids, potentially influenced by bias, was a notable exception. These findings hint at possible statistical significance in larger studies. Inspiringly, the survival of more preterm infants did not correspond to poorer HRQoL and physical

health outcomes. Our study highlights the heterogeneity within the EP-born population, illustrating the importance of personalised, adult follow-up care. Healthcare professionals should be aware of this variability among adults born EP, as some may need extra support into their thirties and beyond.

To our knowledge, no long-term interventional studies aimed at improving long-term outcomes for individuals born EP, have specifically targeted improving and optimising HRQoL. Such studies should involve ongoing assessment of longitudinal HRQoL, including also comparisons of outcomes across different eras, an approach necessary to capture developmental aspects induced by the evolving practices in our NICUs.

4.1 | Strengths and limitations

The major strengths of this study were the longitudinal population-based and controlled design, a relatively high follow-up rate, and assessment at two time points in early adult age. The participation rate was comparable to other follow-up studies with similar study groups.[32] The cohorts were from a well-defined geographic area, with free access to healthcare from all children, reducing the problem of selection bias and influence from socioeconomic factors. We used validated questionnaires, and the SF-36 has been reported the most used HRQoL questionnaire for adults born preterm.[9] Furthermore, this measurement can point at different HRQoL domains that might be most challenging for the EP-born population.

Limitations of the study were the relatively low number of participants and from only one country, possibly influencing the generalisability of the findings. The low number of subjects increases the risk of type II errors, that is failure to reject a null hypothesis that is actually false. Therefore, we have chosen to discuss consistent, albeit non-significant, differences in outcomes between the 82–85 and 91–92 cohorts as they reached their mid-twenties. Replicating this study in lager populations and particularly in low or middle-income countries, would be an important contribution to the research in this field. Another limitation was inadequate statistical power to examine all potential predictors. We chose to control for postnatal steroids, maternal education, and gender. The use of two different questionnaires prevented direct comparisons between the two age points, despite the CHQ-CF87 questionnaire being derived from the SF-36 and having similar domains.

5 | CONCLUSION

There were no significant differences in self-reported HRQoL between subjects of similar age born extremely preterm nearly a decade apart (during the 1980s and early 1990s), that is before and after transformative changes in neonatal care, such as the introduction of surfactant. This pattern was observed both at 18 years and when the participants reached their mid-twenties. However, when in their mid-twenties, we noticed non-significant tendencies for poorer scores in preterm born in the 1980s compared to the 1990s, hinting at potential positive long-term effects from developments in neonatal care.

AUTHOR CONTRIBUTIONS

Merete Røineland Benestad: Conceptualization; investigation; writing – original draft; writing – review and editing; formal analysis. **Jorunn Drageset:** Writing – original draft; writing – review and editing. **Maria Vollsæter:** Writing – review and editing; investigation; project administration; supervision; writing – original draft. **Karl Ove Hufthammer:** Formal analysis; writing – review and editing. **Thomas Halvorsen:** Conceptualization; writing – original draft; writing – review and editing. **Bente Johanne Vederhus:** Writing – original draft; writing – review and editing; methodology; conceptualization.

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MB conceptualised and designed the study, collected and validated data, conducted initial statistical analyses, and drafted the original and final drafts. BV conceptualised and designed the study, developed the data collection instruments, drafted the initial manuscript, and revised the manuscript. JD drafted the initial manuscript and also contributed to manuscript revisions. MV supervised data collection, critically reviewed the manuscript for important intellectual content. TH designed the data collection instruments, collected data, and reviewed and revised the manuscript. KOH supervised and conducted advanced data analysis and interpretation, and critically reviewed the manuscript. All authors approved the final manuscript as submitted. We thank the participants for their generosity in participating in our ongoing study for many years.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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