Health-related quality of life and mental health after extreme preterm birth

A population-based cohort study of long-term consequences of prematurity

Merete Røineland Benestad

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2024

UNIVERSITY OF BERGEN

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Date of defense: 18.06.2024

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Year: 2024
Title: Health-related quality of life and mental health after extreme preterm birth

Name: Merete Røineland Benestad
Print: Skipnes Kommunikasjon / University of Bergen

Scientific environment

The research presented in this thesis was developed as part of my PhD programme at the Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen, Norway. It was based on regional cohorts of young adults who were born extremely preterm in the 1980 and 1990s and who participated in a longitudinal project called Project Extreme Prematurity. The primary research environment was the research group WestPaed Research, which is associated with the Children and Youth Clinic at Haukeland University Hospital, Bergen, Norway.

My primary supervisor for this PhD project was Associate Professor Bente Johanne Vederhus, with co-supervision provided by Professor Jorunn Drageset.

Statistical analyses for the study presented in Paper I was conducted in collaboration with Professor Geir Egil Eide. For studies in Papers II and III, statistical analyses were carried out in partnership with Karl Ove Hufthammer. Both are biostatisticians from the Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway.

This PhD project was funded by the Western Norway Regional Health Authority.

Acknowledgements

In 2017, I had the privilege of joining the research group of Project Extreme Prematurity at the Children and Youth Clinic at Haukeland University Hospital where I worked as a research nurse with children and young adults who were born extremely preterm. This research group was conducting follow-ups on three cohorts of young adults and adults born preterm. At that time, Thomas Halvorsen and Maria Vollsæter were about to commence the third follow-up. I was fortunate to have the opportunity both to work in the neonatal intensive care unit (NICU) and to meet adults who were born extremely preterm themselves. This dual role reinforced my commitment in understanding the best care practices for these individuals and sparked my curiosity about how we can support them throughout their lives.

Bente Vederhus encouraged me to apply for PhD funding and to continue what she had commenced through her PhD work. I feel deeply privileged that both Bente and Thomas had faith in me to undertake this research work. Bente became my primary supervisor, providing invaluable guidance and encouragement throughout the whole process. I am profoundly grateful for all the discussions we had along the way. Although it has been challenging work, I feel immensely privileged to have been given this opportunity.

Jorunn Drageset was my co-supervisor. I thank you for all the time you have spent in pushing me to see the bigger picture and leading me on the right track. Thank you for having faith in me.

Thanks to Thomas and Maria, my co-authors, for sharing your knowledge and inspiring academic talks. Professor Geir Egil Eide and Karl Ove Hufthammer at the Centre for Clinical Research were my statistical supervisors. Thank you both for being patient with me and teaching me.

Thanks to all my colleagues over the years. I am especially grateful for the enjoyable lunches and enriching discussions on the sixth floor of ‘Glasblokken’. A special note of thanks to Tonje Bårdsen—we began as colleagues, but your support has been invaluable. Our many discussions, shared experiences as PhD students, and mutual inspiration have been crucial, particularly during challenging times and in celebrating the positive moments. I also want to express my gratitude to Ingvild

Bruserud and Mette Engan for their insightful discussions and unwavering support throughout this journey.

I am grateful to have had the opportunity to be part of the multidisciplinary research groups WestPaed Research and ‘Forskningsnettverk for pasientrapporterte data’ (Research Network for Patient-Reported Data) at Haukeland University Hospital, and ‘Helsevitenskap og erfaringsforskning’ (Health Science and Experimental Research) at University of Bergen. My participation in various meetings within these groups has provided inspiring and educational discussions, enriching my research experience.

Thanks to the Children and Youth Clinic for granting me the opportunity to carry out my PhD project at the department. Special thanks go to Helle Milde, former unit manager of NICU, and Ansgar Berg, former head of Department of Pediatrics, who both made it possible for me to undertake this work. I am also grateful for the financial support provided by Western Norway Regional Health Authority.

Thank you to all the preterm- and term-born individuals for your invaluable participation in these studies. Your involvement was essential, and without you, this research would not have been possible.

Lastly, I would like to express my heartfelt gratitude to my family and friends. Throughout this journey, you have been my pillars of strength, offering unwavering support and care. I want to extend special thanks to my fiancé for not only taking exceptional care of our child, but also motivating me to dedicate myself to my research work and this thesis. Your sacrifices and encouragement have been invaluable, and I am eternally grateful for your steadfast support.

March 2024

Merete R. Benestad

Abstract

Background: Individuals born extremely preterm (EP) are at significant risk of a spectrum of long-term sequelae, potentially affecting their health-related quality of life (HRQoL) and mental health into adulthood.

Aims: To examine the development of self-reported HRQoL and mental health in EP-born subjects, from young adulthood to the fourth decade of life, compared to term-born controls; to assess differences in HRQoL between two EP-born cohorts.

Methods: This was a longitudinal follow-up study of two Norwegian population-based cohorts born at gestational age of ≤28 weeks or with birthweight of ≤1000 g during the periods of 1982–5 and 1991–2 (the 1980s and 1990s cohort, respectively), including term-born controls. Assessments were conducted with use of questionnaires on self-reported HRQoL, subjective health complaints, and mental health.

Results: The study findings revealed that EP-born individuals from the 1980s cohort reported lower HRQoL, regardless of disabilities. This trend persisted up to the age of 34 years and was particularly evident in mental health domains. EP-born adults from the 1990s cohort had more mental health problems, particularly internalizing problems, when compared to term-born controls, and yet the overall HRQoL was similar in both groups. From the age of 18 to 27 years, results showed worsening scores for internalizing problems in the EP-born group. Comparison between the two birth cohorts revealed no statistically significant differences in HRQoL at the age of 18 years or in participants' mid twenties. However, in their mid twenties, EP-born participants from the 1980s cohort scored numerically lower in the domains of vitality, physical functioning, and role–emotional.

Conclusions: EP-born participants from the 1980s cohort reported poorer HRQoL than term-born controls, a trend which persisted from young to later adulthood, regardless of disabilities. In contrast, EP-born subjects from the 1990s cohort reported similar HRQoL to term-born controls, and yet experienced a notable increase in mental health problems from the age of 18 to 27 years, exceeding those observed in term-born controls. No significant differences in HRQoL were observed between the two birth cohorts (i.e. 1980s vs 1990s), although the 1980s cohort tended to score lower on reaching their mid twenties.

Sammendrag

Bakgrunn: Individer født ekstremt prematurt (EP) har en betydelig risiko for et spekter av langvarige følgetilstander, som potensielt kan påvirke deres helserelaterte livskvalitet (HRLK) og mental helse inn i voksen alder.

Mål: Undersøke utviklingen av selvrapportert HRLK og mental helse hos EP-fødte personer, fra 18 års alder til midten av 30-årene, sammenlignet med kontroller født til termin. Undersøke forskjeller i HRLK mellom to EP-fødte kohorter.

Metoder: Longitudinell oppfølging av to norske populasjonsbaserte kohorter født med en gestasjonsalder ≤28 uker eller med en fødselsvekt ≤1000 gram i periodene 1982-85 og 1991-92 (1980- og 1990-kohortene), inkludert terminfødte kontroller. Vurderingene involverte spørreskjemaer om selvrapportert HRLK, helseplager og mental helse.

Resultater: EP-fødte kohorten fra 1980-tallet rapporterte lavere HRLK, uavhengig av funksjonshemninger. Trenden vedvarte opp til 34 års alder og var spesielt tydelig i domener relatert til mental helse. I 1990-kohorten hadde EP-fødte voksne mer problemer med mental helse, spesielt internaliserende vansker, sammenlignet med kontroller, men deres generelle HRLK var lik. Fra 18 til 27 år forverret internaliserende vansker seg i EP-gruppen. Sammenligning av de to kohortene viste ingen statistiske forskjeller i HRQoL ved 18 år eller i midten av tjueårene, men i midten av tjueårene hadde 1980-kohorten numerisk lavere i domenene vitalitet, fysisk funksjon og rolle-emosjonelle.

Konklusjoner: I 1980-kohorten viste EP-fødte deltakere lavere HRLK enn kontroller, dette vedvarte fra ung til senere voksen alder, uavhengig av funksjonshemninger. EP-fødte kohorten fra 1990-tallet liknende HRLK-nivåer til kontroller født til termin, men opplevde en økning i mentale helseproblemer fra 18 til 27 år, som oversteg de som ble observert i kontroller født til termin. På tvers av de to fødselskohortene (1980-tallet vs. 1990 tallet) ble det ikke observert signifikante forskjeller i HRLK, selv om 1980-kohorten hadde en tendens til å skåre lavere ved midten av 20-årene.

List of Publications

Merete Røineland Benestad, Jorunn Drageset, Geir Egil Eide, Maria Vollsæter, Thomas Halvorsen, Bente Johanne Vederhus

Development of health-related quality of life and subjective health complaints in adults born extremely preterm: a longitudinal cohort study.

Health Qual Life Outcomes ***20****, 112 (2022).*

https://doi.org/10.1186/s12955-022-02018-5

Merete Røineland Benestad, Jorunn Drageset, Karl Ove Hufthammer, Maria Vollsæter, Thomas Halvorsen, Bente Johanne Vederhus

Long term follow-up of self-reported mental health and health-related quality of life in adults born extremely preterm.

Early Human Development 173 (2022): 105661.

https://doi.org/10.1016/j.earlhumdev.2022.105661

Merete Røineland Benestad, Jorunn Drageset, Karl Ove Hufthammer, Maria Vollsæter, Thomas Halvorsen, Bente Johanne Vederhus

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

Acta Acta Paediatr. 2024; 00: 1–10.

https://doi.org/10.1111/apa.17146

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Abbreviations

ADHD	attention-deficit/hyperactivity disorder
APIC	Adults Born Preterm International Collaboration
ASD	autism spectrum disorder
ASEBA	Achenbach System of Empirically Based Assessment
ASR	Adult Self-Report
BPD	bronchopulmonary dysplasia
BW	birthweight
CHQ-CF87	Child Health Questionnaire Child Form-87
CI	confidence interval
CP	cerebral palsy
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders*, fourth edition
ELBW	extremely low birthweight
EP	extremely preterm
FCDC	family-centred developmental care
FEV_1	forced expiratory volume in 1 second
GA	gestational age
HBSC-SCL	Health Behaviour in School-aged Children—Symptom Check List
HRQoL	health-related quality of life
HUH	Haukeland University Hospital
HUI3	Health Utilities Index Mark 3
ICD-10	International Classification of Diseases, tenth revision
IVH	intraventricular haemorrhage
MICE	multiple imputation by chained equations
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
NIDCAP	Newborn Individualized Developmental Care and Assessment Program
PROM	patient-reported outcome measure
PVL	periventricular leukomalacia
QoL	quality of life
RDS	respiratory distress syndrome

RECAP	Research on European Children and Adults Born Preterm (project)
ROP	retinopathy of prematurity
RQ	research question
SD	standard deviation
SES	socio-economic status
SF-36	Short Form 36-Item Health Survey
SGA	small for gestational age
VLBW	very low birthweight
VP	very preterm
WHO	World Health Organization
YSR	Youth Self-Report

Contents

1. General introduction

In 2024, pregnant women in Norway who are in labour at 23–24 weeks' gestation will encounter a healthcare system fully dedicated to protecting the life of their unborn child (1). In Norway, as in most high-income countries, infants born preterm now have access to high-level neonatal intensive care units (NICUs) equipped with advanced technology and staffed by highly trained personnel, with provision of a comprehensive range of pharmacological treatments (2). While such level of advanced care was not available in the early 1980s (3), subsequent progress in perinatal care throughout the decade, including the development of novel technologies and pharmacotherapeutic approaches, as well as a better understanding of the specific needs of preterm infants, has led to a remarkable improvement in survival of infants born increasingly more premature (4). As a result, from the 1990s onwards, the mortality rate for extremely preterm (EP) and extremely low-birthweight (ELBW) infants have significantly declined (3, 5).

As we now enter 2024, individuals born EP in the early 1980s are starting to turn 40, and we need to understand how this group copes with independent adult life. Research indicates that adults born EP face an elevated risk for a variety of non-infectious diseases (6, 7), as well as an increased likelihood of early death in adulthood (8). Studies on health-related quality of life (HRQoL) have yielded conflicting results (9). HRQoL encompasses the connections among a person's health status, functional abilities, and self-reported well-being, and is recognized by established health organizations and institutions as a crucial metric of health (10).

Previous research found poorer HRQoL scores in ELBW preterm school-aged children and adolescents, compared to controls (11). Therefore, it is imperative to gain detailed knowledge of how HRQoL varies in EP/ELBW adults, not only at an individual level as these adults grow and age, but also in relation to advances in neonatal intensive care and improved survival rates over time. It is important to determine whether the challenges faced by this group of individuals during childhood persist into adulthood, whether they catch up with their peers born full term and, ultimately, how they cope with modern adult life stressors. Therefore, there is a strong call for a comprehensive examination of preterm-born individuals, as well as their families, that would encompass not only disease-related factors, but also HRQoL domains, to help gain a broader understanding of the impact of extreme prematurity at birth and extremely low birthweight on this group (12).

In this context, research should ideally involve direct participation of individuals born preterm themselves through use of self-reported methods to evaluate their HRQoL and mental health. As an important step towards understanding this group's own perspectives, this strategy would not only serve to provide answers to EP-born survivors and their families in relation to the impact of their preterm birth on their health and general well-being and functioning. Further, also facilitate the identification of potential areas where additional support may be required.

To date, the literature on HRQoL in EP-born adults has shown conflicting results reported by various authors. Some studies indicated no differences in HRQoL among individuals born EP compared to their term-born peers, whereas other studies showed significant differences (9, 13–18). It should be noted that only few of these studies included adults aged over 30 years or adults born after the 1980s.

Therefore, the overarching aim of this thesis was to enhance our understanding of the impact of extremely premature birth on self-reported HRQoL, subjective health complaints, and mental health among EP-born adults. Research presented in this thesis also aimed to examine whether significant advances in medical techniques and treatments in the NICU setting during the late 1980s have impacted the HRQoL of individuals born EP in the 1980s compared to those born EP in the 1990s.

2. Introduction to prematurity

2.1 Definition of prematurity

Preterm birth refers to birth before 37 weeks' gestation and is further categorized according to gestational age (GA), as shown in Table 1 (19). If the GA is uncertain, the birthweight (BW) can be used to categorize preterm infants. Table 2 shows the different definitions of low birthweight.

Table 1 Classification of preterm birth

Category	**Definition**
Extremely preterm	<28 weeks' completed gestation
Very preterm	28 to <32 weeks' completed gestation
Moderately preterm	32 to <34 weeks' completed gestation
Late preterm	34 to <37 weeks' completed gestation

Table 2 Classification of low birthweight

Category	**Definition**
Extremely low birthweight	<1000 g
Very low birthweight	<1500 g
Low birthweight	<2500 g

2.2 Epidemiology

Worldwide, the preterm birth rate in 2020 was estimated to be approximately 10% of all births (ranging from 5% in parts of Europe and approximately 10% in the United States to over 20% in parts of southern Asia and sub-Saharan Africa). Of these preterm births, 10% occurred at 28 to <32 weeks' gestation, and 4% at <28 weeks' gestation (20). In the last decade, we saw little decline in the rate of preterm births, being similar in 2010 and 2020 (20). The situation in the United States is particularly alarming, as there has been a rise in the incidence of preterm births, especially among some black communities, with rates approaching those observed in sub-Saharan Africa (21).

In high-income countries with access to advanced neonatal care, survival rates of preterm birth have increased (22, 23). Thus, in Norway, the survival rate of infants born at 22–23 weeks' gestation has increased from 19% in 2009–11 to 59% in 2015–18 (24). Notably, the threshold for active treatment has shifted from a GA of 24 weeks in 1998 to 23 weeks in 2005 (25).

2.3 Risk factors for preterm birth

Preterm birth presents with a complex interplay of risk factors affecting the mother, the placenta, and the fetus (26). Approximately 70–80% of preterm births occur spontaneously and are primarily attributed to two main causes: preterm labour (accounting for 40–50% of preterm births) and preterm premature rupture of membranes (contributing to 20–30%) (27). In rare instances, cervical insufficiency may also lead to spontaneous preterm birth. The remaining 20–30% of preterm births are due to maternal or fetal factors that pose significant threats to the well-being of either the mother or the unborn child, including pre-eclampsia, placenta praevia, placental abruption, fetal growth restriction and multiple pregnancy (27). It is important to note that complications during pregnancy can give rise to both spontaneous and medically-induced preterm births (27). Additionally, certain socio-demographic and environmental factors have been shown to increase the risk of preterm birth, for example smoking and outdoor air pollution (26–28). Still, the mechanisms of preterm birth are not fully understood (26).

2.4 Outcomes of preterm birth

Preterm birth is associated with a range of somatic and psychological challenges. This heightened vulnerability can manifest in various ways such as developmental delays, increased risk of various health complications and a higher likelihood of developing mental health issues throughout life (26). Causal factors include conditions directly related to causes of preterm birth as described earlier, antenatal events and challenges associated with completion of developmental processes ex utero that are naturally designed to occur in utero (26). Paradoxically, treatments essential to the infant's survival may also cause injuries, thereby impairing important developmental processes (27). This complex web of consequences and their potential interactions underscore the significant impacts premature birth can have on an individual's overall well-being. Given that these impacts are more pronounced with decreasing GA, particular attention is warranted in cases of EP and ELBW infants.

2.4.1 Health

Short-term complications of EP birth and ELBW include an increased risk of respiratory conditions such as respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) (29, 30), as well as other conditions including necrotizing enterocolitis (NEC) (30–32), sepsis (33), and neurological conditions such as intraventricular haemorrhage (IVH) (31), periventricular leukomalacia (PVL) (30, 31), and retinopathy of prematurity (ROP) (30, 31, 33). The incidence and severity of these morbidities tend to increase with decreasing GA (30).

Long-term outcomes of EP birth and ELBW have received increasing focus in recent years. These include respiratory problems (34), growth and nutritional issues (35, 36), cerebral palsy (CP) (34), vision and hearing defects (37, 38), epilepsy (39), impaired cognitive function (34, 40), psychiatric disorders (38), and motor impairment (41). In adult life, EP birth and ELBW have been found to be associated with an increased risk of diseases and conditions such as heart failure (6), poor blood glucose regulation (42), chronic lung disease (43), and psychiatric disorders (44, 45). The risk of developing these long-term outcomes tends to increase with decreasing GA at birth (46). Moreover, cardiovascular diseases, diabetes, and chronic lung disease have been associated with an increased risk of death in young adults born preterm (7, 8). However, it is reasonable to bear in mind that although the absolute numbers linked with reported odds ratios and relative risks are rather low, for the majority of preterm-born adults, there is still a low absolute risk of these long-term negative outcomes (44). As an example, a recent Nordic register study revealed substantially higher odds of chronic obstructive pulmonary disease (diagnosis recorded with use of International Classification of Diseases, tenth revision (ICD-10) codes) among EP-born adults, compared to term-born peers, but the actual rates of occurrence were about 1% or lower (47).

Preterm individuals are at increased risk of impaired motor outcomes such as CP. The rate and severity of CP in EP/ELBW infants were found to decrease in cohorts born during the period from 1995 to 2009 (48–50). Other studies observed lower scores in motor skills, as well as in reading and spelling skills, in children born EP or with ELBW when tested at both primary school and secondary school ages, compared to the term-born children (51). Furthermore, a review from 2020 revealed that motor problems, as assessed by using a standardized motor test, continue to be significant even among very preterm (VP) and very low-birthweight (VLBW) individuals who do not develop CP, with a prevalence ranging from 8% to 37% (41).

Further, preterm children are also at risk of cognitive functional problems, social and emotional problems, as well as visual and hearing impairment (52). A recent meta-analysis found that intelligence quotient (IQ) scores were lower in adults born VP or with VLBW (53).

2.4.2 Social functioning

Two meta-analyses indicated that preterm-born adults are less likely to have a romantic partnership (54) and tend to rate their relationships with friends lower, compared to controls (55). In contrast, preterm-born adults were found to perceive their family and partner relationships, along with their work and educational experiences, comparably to those of the control group (55).

Still, the long-term outcomes for EP-born adults remain unclear, as EP survival was very rare four decades ago. Most of the outcomes reported in the literature are from young adults aged around 18–20 years.

2.5 Developments in neonatal intensive care

The landscape of neonatal care has undergone significant transformation with advances in neonatal intensive medicine and care. Specialized NICUs were established and developed between the 1950s and the 1970s, and since have played a significant role in improvement of care and outcomes for premature and critically ill newborns (56).

Several notable advances have contributed to overall improvement in neonatal care. One key milestone was the widespread use of antenatal corticosteroids in the 1980s, a development that has led to a reduction in the incidence of conditions such as RDS and intracranial haemorrhage (57). Surfactant replacement therapy represents another crucial innovative technique, initially described in 1980, which became the standard treatment for RDS in premature infants during the early 1990s (58, 59). This treatment significantly reduced the necessity for invasive respiratory interventions such as mechanical ventilation (60). Also highly important in the respiratory care of these infants was the introduction of pulse oximetry that enabled continuous monitoring of oxygenation, with minimal risk of injury, in premature infants (61, 62).

Moreover, improved understanding of preterm nutrition has led to better feeding strategies, including use of human milk and fortified formulas, to support optimal growth and development (63). More aggressive use of antibiotics has been implemented for treatment of neonatal bacterial infections (64), and efficient nursing procedures has helped towards much improved neonatal intensive nursing care (65).

Over the years, NICU staff have increasingly implemented developmental care practices to support the sensory and developmental needs of premature infants. The Newborn Individualized Developmental Care and Assessment Program (NIDCAP), for instance, focuses on reducing stress associated with NICU care and on improving outcomes for infants (66). Additionally, efforts to minimize noise and light exposure, encourage skin-to-skin contact (kangaroo care), and promote family involvement in patient care have also been important steps as part of advances in neonatal intensive care (67). The concept of family-centred developmental care (FCDC) includes active involvement of families in providing personalized support for their baby, promoting healthy development, and minimizing long-term effects of illness on parent–baby interactions (68).

In contrast with the past, when most infants were cared for in a common open bay in the 1980s, increasingly more NICUs now offer family rooms or single rooms, aligning with the 2017 guidelines from the Norwegian Directorate of Health (2). These guidelines emphasize the importance of parents’ involvement in the care team and maximizing parents’ opportunity to be with their child. further enhancing the care and support for both premature infants and their families. Changes are being implemented with the goal of improving long-term outcomes for preterm individuals as they grow up. These include applying the NIDCAP approach, providing parents with 24-hour access to their infants, and offering education and support to families (69). A randomized controlled trial from Norway demonstrated that an early intervention programme involving parents leads to fewer behavioural problems and enhanced cognitive outcomes in children with birthweight under 2000 g (70, 71).

Medical advance have led to increased survival rates of premature babies, especially among the very youngest. Moreover, there has been a shift in attitudes regarding what should be considered the threshold of viability, with opinions varying across countries and institutions, which could lead to ‘bias by survival’ when comparing outcomes across studies. One might infer from this that earlier cohorts consisted of more mature and robust survivors with better long-term outcomes. However, medical technologies and tools used then were less advanced, which might have had an opposite effect. Improved technology has facilitated the survival of more immature and vulnerable neonates. However, it is hard to infer whether overall outcomes have now improved because improved survival of at-risk babies could also mean increasing health issues.

To fully understand the effects of the numerous changes that have occurred in the NICU setting over the past four decades, both in terms of treatment resources and survival rates, it is essential to track and monitor birth cohorts from various eras into adulthood and possibly beyond into old age. Additionally, conducting these longitudinal follow-ups will enable a more informed assessment of whether EP-born individuals will need support as they grow older into adulthood, and if so, at what age and the type of health support required.

3. Introduction to health-related quality of life and mental health

3.1 Health

The concept of health has evolved over time. Traditionally, definitions have linked health with the absence of illness, but it can also encompass well-being and the ability to function (72).

Different models have been used to describe health. The medical model focuses on disease and disability, and is most widely used in medical research (73). However, in 1948, the World Health Organization (WHO) defined health as '*a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity*' (74). This broader definition includes mental and social well-being, representing a more holistic approach. However, this definition has faced criticism (73, 75, 76). One issue is the term 'complete' in describing well-being, which sets an unattainably high standard, potentially classifying most individuals with normal life challenges and minor health issues as unhealthy for much of their lives. Another criticism addresses the evolution of disease since 1948, noting that the original definition does not seem to account for the increasing prevalence of chronic diseases, under which many people can live relatively normal and productive lives despite ongoing health challenges (76). Regardless of these criticisms, the WHO definition of health continues to be applied and has been used in major health studies, including the RAND Health Insurance Experiment (73, 77).

3.2 Health-related quality of life

HRQoL is a multidimensional concept that encompasses both health aspects and overall quality of life (QoL).

The term 'quality of life' (QoL) has received increasing interest in science. Although QoL lacks a universally accepted formal definition (78), it is nevertheless commonly employed in various fields and can be interpreted differently, depending on the context of its application (79). Ferrans emphasized the need for a clearer understanding of what QoL instruments measure (80), which is supported by other researchers in the field of QoL research (81, 82). Different models exist. The model by Cramer and Spilker categorizes QoL assessment as multidimensional, comprising three hierarchical levels: (1) an individual overall assessment of well-being; (2) evaluation of broader domains such as physical, economic, and social aspects; and (3) detailed examination of the components of each domain such as specific diseases and symptoms (83). The model by Wilson and Cleary (84) links five main determinants of overall QoL: (1) biological and physiological factors; (2) symptoms; (3) functional status; (4) general health perceptions; and (5) overall QoL. Both individual characteristics and environmental factors impact all these determinants. Furthermore, the WHO has developed a QoL instrument known as the WHOQOL (85). The WHO defines QoL as '*an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns*' (86).

In the field of medicine, the term HRQoL is often used to avoid ambiguity in meaning with the more general term 'QoL' (78). However, there is also no consensus regarding the definition of HRQoL.

Despite its loose definition, it is widely acknowledged that HRQoL is multidimensional and its domains may vary across studies. These domains can encompass aspects such as overall health, and physical functioning, psychological functioning and social functioning (78). Physical functioning typically refers to one's capacity to carry out a range of daily activities, including those impacted by physical symptoms arising from either an underlying illness or its associated treatment. Psychological functioning covers a wide spectrum of areas, including emotional states ranging from profound psychological distress to a positive sense of overall well-being, as well as cognitive abilities (87). Social functioning involves both quantitative and qualitative aspects of one's social relationships and interactions, as well as their integration into societal structures (87).

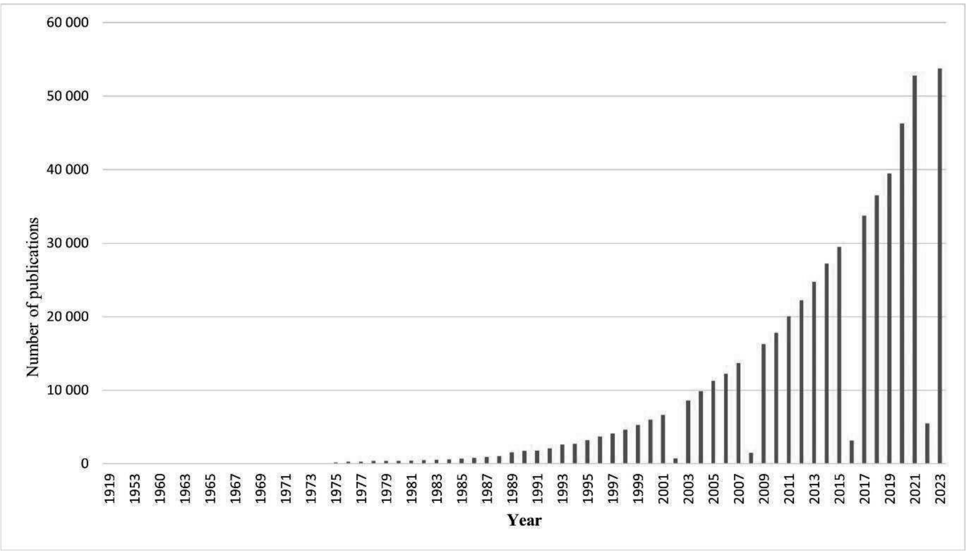


Figure 1 Number of publications referring to HRQoL (published between 1919 and 2023) found on the PubMed database by using the search keyword 'HRQoL' (database accessed on 24 January 2024).

Research on HRQoL started gaining significant attention in the 1970s and early 1980s, with 53,786 articles referring to HRQoL published between 1919 and 2023 found on the PubMed database (Figure 1). During this period, there was a growing recognition of the importance of considering not only the presence or absence of diseases, but also how a disease might affect a person's well-being and QoL (78). Researchers and healthcare professionals began to develop and utilize standardized instruments to assess HRQoL, mostly in the form of structured self-report questionnaires, which consequently contributed to advances in this research field's growth (78). HRQoL assessment has since become an integral part of clinical trials, health economics, and health policy research, leading to continued expansion in its use and importance in healthcare and medicine (78, 84). HRQoL frequently serves as an integral component of patient-reported outcome measures (PROMs). PROMs include tests that measure different aspects of health status directly from the patient's viewpoint, thus eliminating the need for healthcare professionals' interpretation (88).

3.2.1 HRQoL in the general adult population

In the general population, HRQoL appears to follow a similar trend in both young boys and girls, whereas a noticeable decline is observed among girls after they enter puberty (89). In the Norwegian population, the physical component of HRQoL was found to decline across age groups, whereas the mental component improved until the age of 60 years (90). Specifically, depression, anxiety, and loneliness were observed to be more prevalent among the youngest (aged 18–24 years) and the oldest (aged over 75 years). These U-shaped curves generally align well with data from Norwegian and international studies (91–93). Other studies also found women tended to report more mental health issues than men (79).

With respect to socio-economic variables associated with HRQoL, low levels of education and employment opportunities were found to be linked with lower (poorer) HRQoL (94, 95). In contrast, being married or in a cohabiting relationship has been associated with a higher HRQoL (96).

3.2.2 HRQoL in the preterm-born adult population

For the work presented in this thesis, a systematic database search on HRQoL in preterm-born adults was performed with the assistance of staff from the University of Bergen Library. This search identified one review and one meta-analysis, in addition to 25 cohort studies and one qualitative study. Three of these cohort studies included preterm-born individuals born after 1990, whereas participants in the remaining studies were born in the 1970s and 1980s. A higher total of 16 cohort studies of VP/VLBW subjects were identified, compared to nine cohort studies of EP/ELBW participants. Results from these studies are inconsistent, with some studies indicating poorer HRQoL among EP/ELBW and VP/VLBW subjects compared to term-born controls, whereas other studies reported no significant differences (Table 3, pp. 78–83). As already mentioned, data on outcomes in adults born EP remain scarce due to poor survival rates observed 40 years ago.

In a systematic review carried out in 2020, 11 of 18 studies reported no differences in HRQoL between adults born VP or VLWB and term-born controls (9). However, four cohort studies of young adults observed significantly poorer HRQoL in individuals born VP or VLBW compared to term-born controls (14, 97–99). Several studies reported that HRQoL was lower in VLBW individuals, compared with term-born controls, in adolescence and young adulthood (13, 100). Moreover, other data showed that HRQoL tended to deteriorate from adolescence to early adulthood in individuals born preterm (15, 16). It is noteworthy that only one study extended its follow-up beyond 30 years (18).

While a more substantial body of research has focused on subjects born VP/VLBW (13, 99, 100, 104–112), only a limited number of studies have concentrated on participants born EP/ELBW (14–16, 98, 101–103). Of the few studies that focused on the EP-born population, one study compared HRQoL in 18-year-old individuals born EP versus those born at term in the 1990s. Results showed that outcomes were comparable (113). In contrast, another study of EP/ELBW cohort found poorer HRQoL at 25 years compared to their term-born peers (114).

According to the systematic review described above, sex was found to be associated with HRQoL in individuals born VP, with females at risk of experiencing poorer HRQoL (9). However, one study found that VP-born men tended to report poorer HRQoL than their control group, whereas females born VP were more comparable to their controls (97). Additionally, HRQoL appeared to improve into early adulthood among EP-born boys, as reported by their parents, whereas girls' HRQoL seemed to remain relatively stable (113). One study found that small-for-gestational age (SGA) or VLBW women experienced more depressive symptoms (105). Furthermore, HRQoL in individuals born VP/VLBW has been negatively associated with unemployment and poor social functioning (13, 100).

A limited number of qualitative studies have explored HRQoL in this population. One study from Germany (115) conducted in-depth interviews of preterm adults, and found that the majority of participants still had concerns regarding prematurity affecting their daily lives and reported both physical and mental health sequelae. In contrast, a mixed-method study conducted in Canada with interviews of adults born VP found similar quantitative results in both the VP-born group and term-born controls. In response to open-ended questions, VP-born individuals perceived their health as poorer than the general population (116).

In summary, published data on HRQoL in adults born preterm have been inconsistent, with some studies indicating poorer HRQoL in EP/ELBW or VP/VLBW individuals compared to term-born controls, and others reporting no significant differences between the populations. Research on EP births is less common, with a greater number of studies focusing on VP/VLBW individuals. Additionally, factors such as sex and employment status have been linked with HRQoL, with females born very preterm at risk of experiencing poorer HRQoL. Negative associations have also been found between HRQoL and unemployment and poor social functioning in this population.

3.3 Mental health

3.3.1 Mental health

The WHO defines mental health as '*a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community*' (117). In other words, mental health issues may affect a person's thoughts, perceptions, feelings, and behaviours. This is a wide definition, however. When assessing for mental health outcomes, these can include more general outcomes (i.e. internalizing or externalizing problems) to more specific outcomes (i.e. anxiety, depression, eating disorders, and attention-deficit/hyperactivity disorder (ADHD)) (118). Internalizing problems include symptoms of anxiety, depression, and poor social functioning. Externalizing problems include rule-breaking and aggressive behaviour (119). Mental health is also an essential component of HRQoL (78).

Mental health can be examined by using various methods such as clinical interviews and self-reported questionnaires. Research work presented in this thesis focused on self-reported mental health problems. The Youth Self-Report (YSR) and Adult Self-Report (ASR), both part of the Achenbach System of Empirically Based Assessment (ASEBA), are well-established questionnaires widely used in research to investigate self-reported mental health problems. These instruments assess for internalizing, as well as externalizing, problems (119).

3.3.2 Mental health in the general adult population

According to the WHO, mental health issues are common in the general adult population (117) and vary across different age groups. A study from Oslo, Norway, noted that 33% of a randomly selected group of adults aged 18–65 years had experienced mental disorders in the past 12 months (120). In a study from the United States, the authors found that approximately half of the participants had experienced a mental health disorder at some point in their lives (121).

A European review found that 27% of adults aged 18–65 years suffered from at least one mental disorder (122). As mentioned in Section 3.2.1, younger adults tend to experience higher rates of mood disorders such as depression and anxiety, whereas older adults may confront issues related to loneliness or cognitive decline (92, 123).

Sex differences also play a role in mental health. Previous studies showed that women exhibited a higher lifetime prevalence of mood or anxiety disorders compared to men (122, 124). In the general population, women were found to be more prone to internalizing problems, whereas males tended more to exhibit externalizing problems (125).

3.3.3 Mental health in preterm-born adults

In the work presented in this thesis, a systematic database search on mental health in preterm-born adults was conducted, with the support from the University of Bergen Library staff. In total, two meta-analyses and 20 cohort studies were identified (Table 4, pp. 84–87). The birth years of subjects in those studies spanned from the 1970s to the 1990s, with a greater focus on VP/VLBW than on EP/ELBW individuals. Findings predominantly indicated an increased risk of mental health problems, particularly internalizing issues, in preterm-born adults, although outcomes varied, with some studies reporting no significant differences compared to term-born controls (Table 4, pp. 84–87). Challenges in comparing these results arise from methodological differences in, for instance, measurement techniques and study populations. Notably, a meta-analysis conducted in 2017 highlighted higher rates of internalizing and antisocial problems in young adults born very preterm compared to their term-born controls (126). Scandinavian registry studies further underscore the increased risk of mental health disorders associated with reduced GA, emphasizing the complexity of understanding mental health trajectories in this population (38, 127).

Individuals born VP or VLBW appear to face a heightened risk of disorders such as autism spectrum disorder (ASD), ADHD, and anxiety and mood disorders, compared to their term-born controls (128–130). Use of psychotropic medications has also been found to be elevated among EP-born and VLBW individuals (118).

A previous study of self-reported mental health problems among preterm-born men and women observed fewer issues related to intrusive behaviours, as well as a higher prevalence of avoidant personality problems, in this group compared to the control group (126). The same study also found that these differences were more pronounced among preterm-born women compared to preterm-born men (126). Thus, there are indications of significant gender-related differences in mental health problems among the preterm-born population.

In sum, several studies have suggested that young adults born VP or VLBW have an increased risk of developing mental health problems and psychiatric disorders, as well as of psychotropic medication use (118, 126, 128–130). However, a recent systematic review suggested that it is still uncertain whether EP/VLBW adults, in comparison to term-born controls, are at increased risk of mental health disorders or symptoms (118). An Australian cohort study (131) found that both EP/ELBW adults and controls born in the 1990s presented with similar mental health outcomes, which could suggest a potential improvement in mental health in younger preterm-born cohorts. Thus, there might be differences in the risk of developing mental disorders or symptoms based on the birth time period (i.e. pre- vs post-1990s) (118, 131).

3.3.3.3 Possible associations between preterm birth and mental health problems

Several studies have explored potential mechanisms underlying mental health outcomes in preterm-born adults. One study suggested that impaired brain development, as indicated specifically by reduced local gyrification index (which is a measure of degree of folding across the cortical surface), may be linked with adverse mental health outcomes (132). Another study established a connection between mental health and exposure to maternal mood and anxiety disorders among ELBW individuals (133). A higher prevalence of internalizing problems was found in survivors of ELBW who presented with elevated afternoon cortisol levels, suggesting disruption in the developing infant's hypothalamic–pituitary–adrenal axis functioning (134).

3.4 Subjective health complaints

Subjective health complaints serve as a critical measure of individual well-being, capturing personal burdens and experiences (135). Furthermore, somatic symptoms have been shown to be a predictor of mental illness in adulthood and serve as a significant indicator of potential mental health problems (136). Subjective health complaints are highly prevalent in the general population (137–139), with women reporting more complaints than men, as demonstrated in a Norwegian cross-sectional study (137). A study of subjective health complaints in EP-born subjects reported an increase in psychological subjective health complaints from the age of 17 to 24 years (16). However, knowledge of subjective health complaints in the preterm-born population remains limited.

3.5 Rationale for this thesis

The existing literature has given us valuable knowledge of the health challenges faced by EP-born adults. Perinatal medicine and neonatal intensive care have continuously evolved over the past 3–4 decades, with advances in nearly all aspects of care. To comprehensively understand both the negative and positive long-term effects of the evolving neonatal intensive care, it is necessary to follow up cohorts of EP-born individuals into not only early, but also later, adulthood. There are still gaps in our current knowledge of HRQoL, subjective health complaints, and mental health in EP-born adults. As new generations of individuals born EP grow and enter adulthood, continuous monitoring of their HRQoL and mental health becomes crucial. The research work presented in this thesis aimed to achieve precisely this objective. Such approach would serve as a significant measure of the care quality delivered in NICUs.

(Date of completed literature search: 22 January 2024)

4. Study aims and research questions

The overall aim of the work presented in this thesis was to gain a better understanding of self-reported HRQoL and mental health in adults born EP. The specific study aims and research questions (RQs) are detailed below.

- **Paper I:** The first aim of this study was to investigate self-reported HRQoL and subjective health complaints in 34-year-old individuals born EP in the period of 1982–5, by comparing study participants with and without disabilities to term-born controls. The second aim was to examine and compare the longitudinal changes in HRQoL from the age of 24 to 34 years, and subjective health complaints at the age of 17, 24, and 34 years.
  - **RQ1:** Do HRQoL and subjective health complaints differ between 34-year-old adults born EP during the 1980s and term-born controls?
  - **RQ2:** Do EP-born adults with and without disability report different HRQoL and subjective health complaints compared to term-born controls?
  - **RQ3:** Is the development of HRQoL and subjective health complaints different between EP-born adults and term-born controls?
- **Paper II:** The first aim of this study was to investigate whether self-reported HRQoL and mental health of adults in their mid twenties, born EP during 1991–2, differ from matched term-born controls. The second aim was to examine the longitudinal development of self-reported mental health from the age of 18 to 27 years.
  - **RQ4:** Do HRQoL and mental health differ between adults in their mid twenties born EP during the 1990s and term-born controls?
  - **RQ5:** Is the development in mental health from youth to the mid twenties different between EP-born adults and term-born controls?
- **Paper III:** The aim of this study was to compare self-reported HRQoL between two birth cohorts of participants born EP in two distinct eras of neonatal care (namely the 1980s and the early 1990s), with evaluations conducted at the age of 18 years and again in the mid twenties. Matched term-born controls were included to illustrate potential shifts in HRQoL during this two periods that could result from societal changes rather than from preterm birth.

- **RQ6:** Do EP-born adults from two distinct birth cohorts have different HRQoL?

5. Subjects and methods

5.1 Design

The research work presented in this thesis utilized data from two population-based cohorts of adults born EP in a defined Norwegian region. Cohort participants were individually matched with term-born control subjects. A retrospective longitudinal cohort design was applied, as cohort identification was performed retrospectively from birth protocols from the neonatal department, but before follow-up data were collected.

5.2 Study population

The study reported in Paper I involved a cohort born between 1982 and 1985. The study presented in Paper II focused on a cohort born between 1991 and 1992, and the study described in Paper III included both cohorts. In all three studies, the cohorts were matched with term-born controls.

5.2.1 Preterm-born subjects

The participant recruitment took place in 2001–2, as detailed in a previous doctoral thesis (140). Cohort participants were born in two distinct periods: January 1982 to December 1985 (referred to as the 1980s cohort), and February 1991 to June 1992 (referred to as the 1990s cohort). These two cohorts included all infants born within a defined area of Western Norway at a GA of ≤28 weeks or with a birthweight of ≤1000 g. Haukeland University Hospital (HUH) was the only institution in the region admitting, and providing care to, EP-born infants. Identification of these children was based on admission protocols from the NICU at HUH.

At the time of inclusion, HUH had an annual birth rate of approximately 6700. Of these, 81 EP-born infants from the 1980s cohort and 47 from the 1990s cohort were admitted to the NICU during their respective inclusion periods. At the first follow-up, 51 infants from the 1980s cohort and 35 from the 1990s cohort were alive. Survival rates at hospital discharge were 63% for the 1980s cohort and 75% for the 1990s cohort.

Determination of the GA was based on the number of completed weeks since the last menstrual period, the GA predicted by ultrasound scanning conducted before 21 weeks' gestation, and postnatal paediatric examination. In cases of discrepancy, GA given by ultrasound assessment was preferred if the GA differed by >2 weeks from its date-based estimate, whereas GA obtained from postnatal paediatric examination was favoured if it differed by 4 weeks or more from either the date- or ultrasound-based estimate. For nine of the 346 reviewed cases, determining the GA at birth proved challenging, and the final decision was entrusted to an external expert in fetal medicine and intrauterine development (140).

5.2.2 Term-born control subjects

Individually matched term-born control subjects were recruited at the time of the first follow-up for each EP-born participant. In both cohorts, term-born individuals of the same sex, with a GA of ≥37 weeks and a BW of between 3000 and 4000 g, who were born closest in time to their corresponding EP-born index subjects, were identified from birth records from the same delivery unit. If a term-born individual declined to participate, we approached the next term-born individual who was born closest in time to the EP-born index subject. This process was repeated until a suitable match was secured. On average, 1.3 term-born controls were contacted for each EP-born participant to assemble a complete matched control group.

Some exclusion criteria were established. Firstly, participants residing beyond a 1-hour travel radius from the hospital at the first follow-up were excluded. Secondly, individuals with a diagnosis of mental illness or physical disability likely to affect their performance during testing were also excluded.

5.3 Methods

5.3.1 Data collection

The research work presented in this thesis was undertaken as part of a larger study conducted by the WestPaed research group at the Department of Pediatrics, HUH. The primary focus of this larger study was to assess lung function and exercise capacity among adults born EP.

The follow-up timeline and mean age of participants are illustrated in Figure 2.

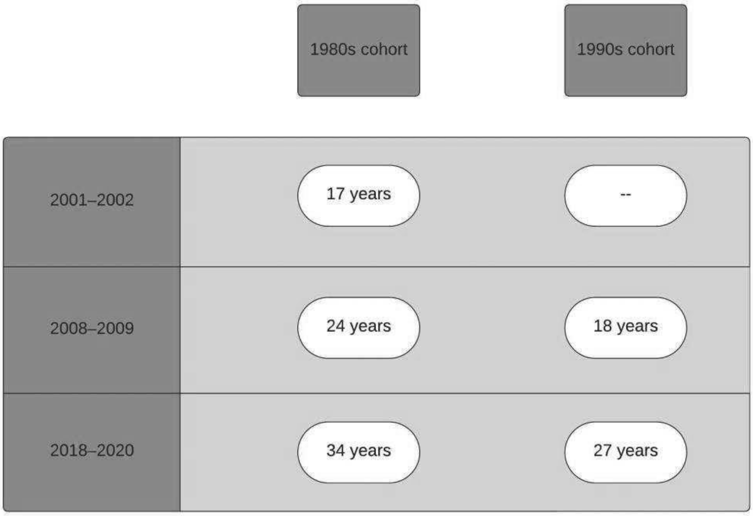


Figure 2 Follow-up timeline and mean age of participants of the two cohorts described in this thesis (NB the 1990s cohort participated also in the 2001–2 follow-up, but the data are not included in this thesis).

Participants from both cohorts completed questionnaires at HUH where they also underwent examinations. A small number of subjects (the 1980s cohort, $n = 4$; the 1990s cohort, $n = 1$) completed the questionnaires at home and returned them by post at the last follow-up (2018–20).

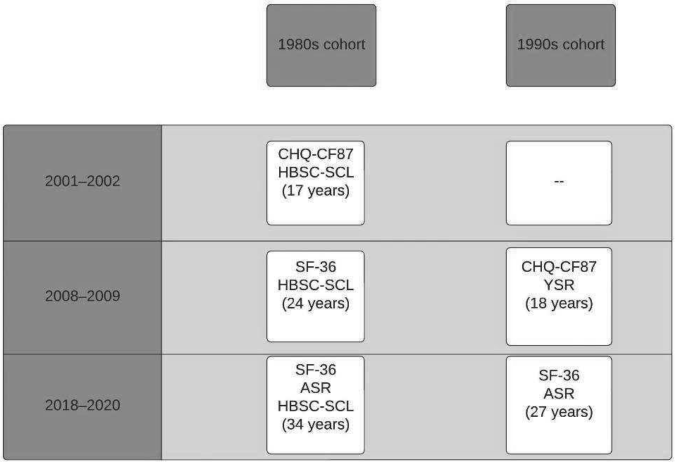
Questionnaire data and other participant information were manually entered into a data file with assigned variables determined by the operator. To ensure accuracy, all data underwent a double-entry process, with two individuals independently checking or entering the data twice.

5.3.1.1 User participation/involvement

During the study planning phase of the last follow-up (2018–20), two former EP-born adults who were part of the previous follow-ups, provided valuable feedback and actively participated in study planning.

5.3.2 Health-related quality of life measures

The research work described in this thesis primarily focused on assessing HRQoL, mental health, and subjective health complaints in EP-born subjects as the key outcomes. For this purpose, we utilized the following questionnaires: Child Health Questionnaire Child Form-87 (CHQ-CF87); Short Form 36-Item Health Survey (SF-36); YSR; ASR; and Health Behaviour in School-aged Children—Symptom Check List (HBSC-SCL). An overview of age-appropriate questionnaires used for this research is illustrated in Figure 3 and detailed further below.



	1980s cohort	1990s cohort
2001–2002	CHQ-CF87 HBSC-SCL (17 years)	--
2008–2009	SF-36 HBSC-SCL (24 years)	CHQ-CF87 YSR (18 years)
2018–2020	SF-36 ASR HBSC-SCL (34 years)	SF-36 ASR (27 years)

Figure 3 Overview of questionnaires used. ASR, Adult Self-Report;CHQ-CF87, Child Health Questionnaire Child Form-87; HBSC-SCL, Health Behaviour in School-aged Children—Symptom Check List; SF-36, Short Form 36-Item Health Survey; YSR, Youth Self-Report. (NB the 1990s cohort participated also in the 2001–2 follow-up, but the data are not included in this thesis.)

5.3.2.1 Child Health Questionnaire Child Form-87 (CHQ-CF87)

The HRQoL was assessed in study participants at the age of 18 years by using the CHQ-CF87 questionnaire, a generic instrument designed for individuals aged 10–18 years (141) (for details, see Appendix I). For the purpose of this study, the validated Norwegian version of the questionnaire was used (142). This comprehensive tool evaluates physical, emotional, and social well-being in children and adolescents on 87 items distributed across 12 scales, as follows: 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) (Table 5a). The last item 'change in health' was not used in this study. Each item features 4–6 sequential response levels, ranging from 'very often' to 'not at all', with each level assigned a corresponding numerical score. The recall period was defined as the preceding 4 weeks. The item raw scores within each scale were summarized and transformed into a sum score ranging from 0 (indicating poor HRQoL) to 100 (indicating optimal HRQoL).

Table 5a Overview of domains/scales in HRQoL questionnaire

HRQoL			
Domains/scales	**Questionnaires**	**Number of items**	**Comment**
Physical functioning	CHQ-CF87 SF-36	9 10	Scores transformed into a scale from 0 to 100, with higher scores indicating better functional health and well-being
Role emotional	CHQ-CF87 SF-36	3 3	
Role behavioural	CHQ-CF87	3	
Role physical	CHQ-CF87 SF-36	3 4	
Bodily pain	CHQ-CF87 SF-36	2 2	
Behaviour	CHQ-CF87	17	
Mental health	CHQ-CF87 SF-36	16 5	
Self-esteem	CHQ-CF87	14	
General health	CHQ-CF87 SF-36	12 5	
Family activities	CHQ-CF87	6	
Family cohesion	CHQ-CF87	1	
Vitality	SF-36	4	
Social functioning	SF-36	2	

Abbreviations: CHQ-CF87, Child Health Questionnaire Child Form-87; HRQoL, health-related quality of life; SF-36, Short Form 36-Item Health Survey.

5.3.2.2 Short Form 36-Item Health Survey (SF-36)

The HRQoL was measured in participants in their mid twenties and mid thirties by using the SF-36. The SF-36 was originally developed for the Medical Outcomes Study, which included surveys based on a multidimensional model of health that included 40 health concepts (143).

The SF-36 is a generic instrument that assesses self-reported functional health and well-being in eight important health domains that were included in the Medical Outcomes Study: 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) (Table 5a). Responses were rated on a 3- to 6-point ordered response levels, with the preceding 4 weeks as the recall period, except for the two role-functioning domains, which have dichotomized response choices, and for physical functioning and general health, which pertain to current status. For each SF-36 subscale, raw scores were calculated as the average of valid items, provided that at least half of the items in each scale were valid. These scores were then linearly converted to a range of 0 to 100, with higher scores representing enhanced functional health and well-being (144, 145).

Due to changes in the licensing agreement, SF-36 version 1.1 was replaced with RAND-36 at the last follow-up in 2018 (for details, see Appendix II). SF-36 version 1.1 was used at the age of 27 years for the 1980s cohort; RAND-36 was used at the age of 24 years for the 1990s cohort and at the age of 34 years for the 1980s cohort. The RAND-36 questionnaire was originally developed by the RAND Corporation (144). As RAND-36 is comparable to the 36-item SF-36 version 1.1, the SF-36 scoring procedure was applied. The Norwegian version of RAND-36 included slight differences in phrasing, compared to SF-36, reflecting more modern language use, as detailed in Appendix III. For simplicity, RAND-36 is referred to as SF-36 for the research work presented in this thesis.

This generic health measurement evaluates HRQoL outcomes and is not specific to any age, disease, or treatment group (78). SF-36 is the most widely used tool in health surveys for assessing physical functioning, as well as the social and mental components of HRQoL (78), and is a suggested measure for follow-up studies of adults born preterm (146). The questionnaire has been demonstrated to have good reliability and validity (144), including in Norwegian populations (90).

5.3.3 Self-reported mental health measures

5.3.3.1 Achenbach System of Empirically Based Assessment (ASEBA): Youth Self-Report (YSR) and Adult Self-Report (ASR)

Self-reported mental health was assessed by using the validated Norwegian version of the ASEBA, specifically the YSR and ASR (119, 147). These two questionnaires consist of problem items that individuals rate as ‘not true’ (0 point), ‘somewhat or sometimes true’ (1 point), or ‘very true or often true’ (2 points) (Table 5b). A sum score was calculated for each of the eight syndrome scales. Six of these scales were also used to compute two broad group scores: an internalizing score (comprising anxious/depressed, withdrawn/depressed, and somatic complaints); and an externalizing score (consisting of rule-breaking behaviour, aggressive behaviour, and intrusive behaviour). The other syndrome scales (thought problems and attention problems) were not considered components of either the internalizing or externalizing scores, but, in conjunction with the latter, they contributed to deriving a total score. The total score on the YSR/ASR, based on all problem items, represents the overall problem score, where higher scores indicate poorer functioning. The correlation between the YSR and the ASR has been found to be stable and acceptable in both American and Dutch samples (148, 149).

The ASEBA YSR and ASR are reliable, validated, and broadly utilized for assessing social, adaptive, and psychological functioning in youth aged 11–18 years and adults aged 18–59 years (147, 150). These measures are recommended for assessing mental health problems in preterm-born youth and adults (146).

In terms of internal consistency, Cronbach’s alpha for the YSR was reported as $\alpha = 0.65–0.95$ (total) (147). For the ASR, the values were: $\alpha = 0.95$ (total); $\alpha = 0.91$ (internalizing); $\alpha = 0.84$ (externalizing); and $\alpha = 0.81$ (attention problems) (151).

Content validity refers to whether the items comprehensively cover the concept being measured, and is relevant for multi-item scales (152). This has been established for the ASR through various means, including findings that adults with mental health issues scored significantly higher than a control group and/or showed significant loadings on empirically based syndromes (119). The scales were also identified by the expert panel as being highly consistent with *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV). Additionally, criterion validity, which examines the relationship between specific measures (78), has been confirmed by significant associations with all measures.

Construct validity refers to the extent the questionnaire measures the theoretical construct it is intended to measure (78). Construct validity has been demonstrated by comparing the ASR to similar mental health questionnaires in studies conducted in several countries such as Finland, the Netherlands, Turkey, and the United States. These studies revealed significant predictive relationships from child and youth forms to the ASR questionnaire in the general population (119).

Table 5b Overview of domains/scales in mental health

Mental health			
Domains/scales	**Questionnaires**	**Number of items**	**Comment**
Anxious/depressed	YSR ASR	13 18	Higher scores indicate poorer functioning. The total problem score ranges from 0 to 210 for YSR, and from 0 to 240 for ASR
Withdrawn	YSR ASR	8 9	
Somatic complaints	YSR ASR	10 12	
Thought problems	YSR ASR	12 10	
Attention problems	YSR ASR	9 15	
Aggressive behaviour	YSR ASR	17 15	
Rule-breaking behaviour	YSR ASR	10 14	
Social problems	YSR	11	
Intrusive behaviour	ASR	6	
Internalizing problems	YSR ASR	31 39	
Externalizing problems	YSR ASR	32 35	
Total problems	YSR ASR	112 120	

Abbreviations: ASR, Adult Self-Report; YSR, Youth Self-Report.

5.3.4 Subjective health complaints measure

5.3.4.1 Health Behaviour in School-aged Children—Symptom Check List

Subjective health complaints among participants were assessed by using the HBSC-SCL (for details, see Appendix IV). This instrument evaluates the presence of four somatic symptoms (headache, abdominal pain, backache, and dizziness) and four psychological symptoms (feeling low or depressed, being irritable or bad-tempered, experiencing nervousness, and encountering sleep difficulties) (153). Participants were asked to indicate the frequency at which they had experienced these symptoms in the preceding 6 months. Each item was rated on a 5-point response scale, ranging from ‘daily’ (4 points) to ‘rarely/never’ (0 point). Subsequently, two sub-scores (ranging from 0 to 16 points) and a total sum score (ranging from 0 to 32 points) were calculated, with higher scores indicating a higher number of reported symptoms (Table 5c). The Norwegian version of the instrument, which has been translated and validated, was utilized (154). This version has demonstrated satisfactory reliability in test–retest analyses, with coefficients ranging from 0.70 to 0.80.

Table 5c Overview of domains/scales in subjective health complaints

Subjective health complaints			
Domains/scales	**Questionnaires**	**Number of items**	**Comment**
Somatic subscale	HBSC-SCL	4	Higher scores indicate a higher number of reported symptoms. Scores range from 0 to 16 for somatic subscale, and from 0 to 16 for psychological subscale. The total score ranges from 0 to 32
Psychological subscale	HBSC-SCL	4	
Total score	HBSC-SCL	8	

Abbreviations: HBSC-SCL, Health Behaviour in School-aged Children—Symptom Check List.

5.3.5 Socio-demographic and medical history

Socio-demographic data for both cohorts, such as current educational level, occupation, and living arrangement, were collected by using a custom-made questionnaire based on questions used in Norwegian population studies (available from: http://www.hunt.ntnu.no). Medical history was obtained from interviews with the participants themselves and from hospital records.

5.4 Statistical analysis

Statistical analyses were conducted in collaboration with experienced statisticians at HUH. For studies presented in Papers I–III, descriptive statistics of demographic characteristics were reported by using appropriate summary statistics for continuous and categorical variables. Results were presented in terms of counts, proportions, means, and standard deviations (SDs). To compare birth characteristics between participating and non-participating eligible subjects, Welch's *t*-test and Pearson's chi-square test were employed to assess for potential selection bias in the studies presented in Papers I and II (see Appendix VI for Paper I).

In the study described in *Paper I*, subgroup analyses of EP-born participants were performed, including those with severe disabilities versus those considered healthy. These subgroups were compared to term-born controls by using mean differences and 95% confidence intervals (CIs). Mixed linear models were applied to account for the matched structure (matching by sex and date of birth) of EP-born participants and term-born controls and repeated responses (at 17, 24, and 34 years for assessment using HBSC-SCL, and at 24 and 34 years for SF-36). This approach also allowed for contributions from pairs with missing participation. Mean scores for different domains were entered separately as dependent variables, with age and group entered as independent variables, including an interaction term to assess for potential variation in group differences by age. Analyses were conducted both unadjusted and adjusted for sex, education, and working status.

In the study reported in *Paper II*, to estimate longitudinal differences in mental health (YSR and ASR), linear longitudinal regression models were fitted, with group (EP-born subjects vs term-born controls), age (18 vs 27 years), and group–age interaction as explanatory variables. For each individual, the two error terms at ages of 18 and 27 years were modelled as correlated. Use of a longitudinal model with correlated error terms allowed inclusion of subjects with only partial follow-up data, thereby reducing potential bias from missing data. Some data were missing, particularly at the 27-year follow-up.

In the study presented in *Paper III*, multiple imputation was applied to improve accuracy and statistical power (155). This method is currently considered the best choice in terms of dealing with missing data (152). Multiple imputation by chained equations (MICE) was chosen to replace missing data, thereby minimizing biases (155). Firstly, MICE generates multiple imputed data sets, assigning reasonable values for missing data in each set. Next, a *t*-test was run on each data set, and results pooled across imputations. Missing data included information from some participants at the age of 18 years and others in their mid twenties, and cases in which only some questions were missed. Variables included in the imputation were age, sex, cohort, HRQoL scores, use of postnatal steroids, and maternal education.

Additionally, adjusted regression analyses were performed to assess for potential explanatory factors for HRQoL outcomes in the preterm-born group, including the following predictors: cohort, postnatal steroid administration, sex, and maternal education.

Statistical significance was set at *p*-value of ≤0.05 in all studies presented in Papers I–III. The statistical package SPSS version 26.0 (SPSS Inc., Chicago, IL, United States) was used for analysis in studies described in Papers I and II. R version 4.1.1 and 4.2.1 was additionally used in studies reported in Papers II and III (156).

As the research work presented in this thesis was part of a larger study, statistical power was calculated based on lung function. The initial study design aimed to achieve 90% statistical power for identifying differences >7.5 percentage points in the forced expiratory volume in 1 second (FEV_1) between the EP-born group and the term-born control group. This objective was based on the assumption of normally distributed data and required a sample size of 39 individuals per group. The calculations also took into account a within-group SD of 10 percentage points and a two-sided significance level set at 0.05.

5.5 Ethics

The study complied with the Declaration of Helsinki (157). The study protocol was approved by the Regional Committee for Medical Research Ethics for Western Norway (Protocol no. 2017/628, Appendix V). The primary ethical principles for conducting research include: beneficence; justice; and respect for human dignity and participant authorization (152).

The principle of beneficence refers to 'do no harm' (152). Questionnaires were kept to the shortest length that would still allow addressing the study aims. Participants were also informed that they could contact the research nurse if they had questions or felt emotional after their assessments.

The principle of justice refers to participants' right to fair treatment and their right to privacy (152). Collected data were coded, with a unique number assigned to each participant and used in the questionnaires.

The principle of respect for human dignity and participant authorization refers the right to self-determination and to full disclosure (152). An invitation letter was sent to participants, explaining the study aims and emphasizing that participation was voluntary. Informed written consent was obtained from all participants and, in the case of minors, from parents on the first visit. Participants also gave informed written consent at all follow-ups, and were told of their right to withdraw from the study at any time without having to provide a reason.

6. Summary of results

This section presents the main findings of the studies described in Papers I–III.

6.1 Subjects

The combined flow chart in Figure 4 below illustrates the recruitment of participants for both cohorts.

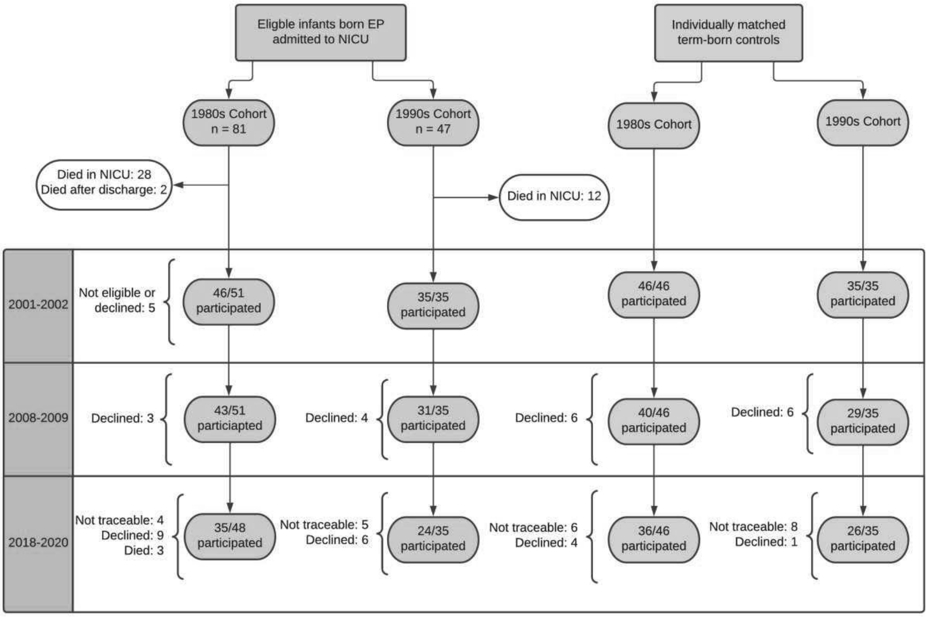


Figure 4 Number of EP-born participants and term-born controls at each stage of the study, from inclusion to the age of 25 years (1990s cohort) and 34 years (1980s cohort).

6.2 HRQoL and subjective health complaints in EP-born participants from the 1980s cohort (Paper I)

This study included the 1980s cohort of EP-born participants born at GA of ≤28 weeks or with birthweight of ≤1000 g. Of the original cohort, 73% of surviving EP-born individuals (35 out of 49) and 78% of term-born controls (36 out of 46) participated in the third follow-up. The subjects were aged 32–36 years and born between 1982 and 1985.

Results showed that EP-born participants who were considered healthy reported statistically significantly poorer mean scores for vitality, role emotional, and mental health, and significantly higher mean scores (i.e. more complaints) for psychological and total health complaints, compared to term-born controls. EP-born participants with severe disabilities reported clinically significant poorer mean scores in all HRQoL domains when compared to term-born controls; a large SD was observed for the domains of physical functioning, role physical, general health, and role emotional (41.1, 51.7, 28.3, and 54.8, respectively). For healthy EP-born participants, the SD was large for the domain of social functioning (30.2). These findings suggest heterogeneity in the group of EP-born participants. No statistically significant differences were found between EP-born subjects with and those without BPD (for details, see Appendix VII).

No statistically significant interactions with age were observed in relation to HRQoL and somatic health complaints. However, statistically significant longitudinal differences in psychological health complaints were evident, with EP-born individuals scoring higher at the age of 24 years and subsequently lower at the age of 34 years.

6.3 HRQoL and mental health in EP-born participants from the 1990s cohort (Paper II)

This study included the 1990s cohort of EP-born participants born at GA of ≤28 weeks or with birthweight of ≤1000 g. The participation rate was 69% (24 out of 35) for EP-born participants, and 74% (26 out of 35) for term-born controls at the age of 27 years. EP-born subjects were found to have higher mental health scores (i.e. more problems) in the areas of internalizing problems, as well as on the syndrome scales of anxiety/depression and withdrawal, compared to term-born controls. Regarding HRQoL, similar scores were obtained in both EP- and term-born groups across most domains, except in the domain of physical functioning where EP-born participants scored lower than term-born controls.

When assessing developmental trends over time from the age of 18 to 27 years, a progressive increase (indicating worsening) in scores was observed for internalizing problems, anxious/depressed symptoms, somatic complaints, and attention problems in the EP-born group. In addition, term-born controls showed an increase in scores specifically for anxious/depressive symptoms over the same time period.

6.4 HRQoL in the 1980s versus the 1990s cohorts of EP-born adults (Paper III)

This study compared HRQoL data between the 1980s cohort and the 1990s cohort when the participants had reached similar ages (i.e. 18 years and mid twenties), to assess for potential cohort effects that might have occurred across these two decades. The participation rates were 90% (77) of EP-born individuals and 93% (75) of term-born controls at the age of 18 years, and 78% (67) of EP-born subjects and 82% (66) of term-born controls in their mid twenties. Both at 18 years and in their mid twenties, EP-born participants from both birth cohorts reported relatively similar HRQoL scores, with no evident differences across the birth decades. However, in their mid twenties, EP-born individuals from the 1980s cohort scored numerically lower (indicating poorer HRQoL) than those from the 1990s cohort in three domains: physical functioning; vitality; and role emotional. In contrast, term-born controls scored consistently across the birth decades in all domains.

When examining the relationship between HRQoL and neonatal factors in both cohorts, postnatal corticosteroid treatment was found to adversely affect HRQoL at the age of 18 years, particularly in the domains of role–physical, self-esteem, and mental health. This negative impact extended into the participants' mid twenties, affecting the domains of social functioning and general health. Additionally, EP-born females at the age of 18 years scored lower in the domains of role emotional, role behavioural, bodily pain, mental health, and self-esteem, with low scores in bodily pain persisting into their mid twenties. Higher maternal education among EP-born participants was linked with improved scores in the domains of role emotional and role–physical at the age of 18 years, but this association did not hold in the subjects' mid twenties.

6.5 Comparison between term-born control group and normative data

Term-born controls showed results comparable to normative data taken from the Norwegian population and the ASEBA Manual (119). These findings are presented in Tables 6 to 8.

Table 6 Mean SF-36 scale scores presented for term-born controls, together with normative data from the Norwegian population, aged in their thirties

SF-36 domains	Term-born controls[a] Mean (SD)	Norwegian normative data[b] Mean (SD)
Physical functioning	94.4 (11.0)	93.5 (12.4)
Role physical	85.7 (32.8)	85.2 (30.8)
Bodily pain	78.5 (22.9)	78.6 (23.6)
General health	75.7 (18.7)	80.2 (19.5)
Vitality	60.3 (19.1)	60.5 (20.0)
Social functioning	89.6 (22.6)	88.4 (19.3)
Role emotional	91.4 (26.0)	88.6 (27.3)
Mental health	79.9 (16.7)	79.6 (14.8)

[a] At mean age of 34 years.

[b] Age range of 30–39 years (90).

Table 7 Mean SF-36 scale scores presented for term-born controls, together with normative data from the Norwegian population, aged in their twenties

SF-36 domains	**Term-born controls**[a] **Mean (SD)**	**Norwegian normative data**[b] **Mean (SD)**
Physical functioning	98.0 (4.8)	95.07 (11.0)
Role physical	92.0 (17.3)	88.10 (27.4)
Bodily pain	86.9 (18.9)	80.97 (22.3)
General health	75.6 (21.5)	80.54 (18.0)
Vitality	63.2 (20.5)	59.65 (18.3)
Social functioning	88.0 (18.6)	89.18 (17.9)
Role emotional	86.7 (30.4)	87.85 (27.0)
Mental health	78.9 (18.7)	78.90 (14.2)

[a] At mean age of 27 years.

[b] Age range of 20–29 years (90).

Table 8 Mean Adult Self-Report (ASR) scale scores presented for term-born controls, aged in their twenties, together with normative data taken from the ASEBA manual

Adult Self-Report	**Term-born controls**[a]	**ASEBA manual normative samples**[b]	
	Mean (SD)	**Mean (men/women)**	**SD (men/women)**
Anxious/depressed	5.6 (5.5)	5.8/6.8	5.7/5.3
Withdrawn	1.7 (1.6)	2.7/2.3	2.4/2.2
Somatic complaints	3.0 (2.8)	2.4/2.8	2.8/2.9
Thought problems	1.2 (1.5)	2.4/2.4	2.3/2.1
Attention problems	5.4 (4.2)	5.2/6.1	5.1/4.1
Aggressive behaviour	2.1 (1.9)	4.7/4.9	4.8/4.7
Rule-breaking behaviour	0.9 (1.3)	3.0/2.4	3.3/2.8
Internalizing problems	10.3 (8.3)	10.8/11.9	8.8/8.6
Externalizing problems	4.7 (3.2)	10.4/9.7	8.3/7.7
Total problems	28.4 (18.9)	38.9/39.3	25.9/23.8

[a] At mean age of 27 years.

[b] Age range of 20–29 years (119).

7. Discussion

The research work presented in this thesis investigated self-reported HRQoL, subjective health complaints, and mental health in adults born EP, by using a range of questionnaires. It specifically studied two birth cohorts longitudinally: one in their mid twenties (i.e. born in the 1990s) and one in their mid thirties (i.e. born in the 1980s). This study differs from existing research on the EP-born population by focusing on these outcomes in cohorts across three distinct stages of their adult life.

Further, these study results would provide valuable information to EP-born adults themselves, as well as to the healthcare community, contributing to a better understanding of the impact of EP birth. Clinical implications of the findings are discussed, and potential areas for future research suggested.

The main results are discussed first, followed by methodological considerations.

7.1 Discussion of main results

7.1.1 HRQoL in EP-born adults

In the 1980s cohort, differences in HRQoL were observed, with poorer scores among EP-born participants at the age of 34 years, compared to term-born controls, particularly in mental health domains (Paper I). Making direct comparisons to other studies is challenging due to variation in measurements, birth years, GA, and inclusion criteria. To the best of our knowledge, this study is among the first to report on HRQoL in EP-born adults aged above 30 years. However, some studies included participants based on birthweight. The HRQoL scores from the 1980s cohort in this study are consistent with results from, for example, a Canadian study of ELBW individuals aged between 29 and 36 years, which assessed HRQoL by using the Health Utilities Index Mark 3 (HUI3) questionnaire (15), and a Norwegian VLBW study which examined HRQoL in VLBW subjects at the age of 32 years by using the SF-36 (18). Together, these findings suggest that EP birth can impact HRQoL in individuals well into their thirties.

The study findings here suggest a significant risk of reduced HRQoL in EP-born adults, which could negatively affect daily functioning (Paper I). Notably, the participants tended to score lower in mental health domains, rather than in physical domains. While this observation aligns with studies of individuals born ELBW/VLBW in the 1980s (13, 18, 103), it contrasts with other studies that found no differences between ELBW/VLBW individuals and term-born controls (101, 102, 111, 112). This prompts the question of whether studies that failed to find such differences enrolled participants with fewer morbidities, in particular studies of VLBW individuals which included participants with birthweight of ≤1500 g. It may also be that these preterm-born individuals did not experience reduced HRQoL, or that different questionnaires were used. Consequently, in consultations with EP-born adults, it would be advisable to follow up on mental health domains of the HRQoL.

On a positive note, the 1990s cohort, born nearly a decade later and aged in their mid twenties, reported HRQoL scores that were similar, or almost similar, to those of term-born controls (Paper II). Of the limited number of studies available for comparison, one cohort study from Australia, that used the HUI3 questionnaire, indicated poorer HRQoL scores in EP/ELBW participants at the age of 25 years (114). The fact that there are only two studies on cohorts from the 1990s, and both based on relatively small groups, underscores the necessity of conducting further research on cohorts born in the 1990s. To overcome this limitation, it is advisable to pursue collaborative efforts that would enable data pooling, similar to initiatives such as the Research on European Children and Adults Born Preterm (RECAP) project and Adults Born Preterm International Collaboration (APIC) (158).

As we turn our attention to more recent developments in neonatal intensive care, it is notable that while overall survival rates have increased for infants born at GA of 23 and 24 weeks, few in this group survive without major neonatal morbidity (58). In this study, the 1990s cohort had non-participants with severe disabilities. Therefore, considering the similar HRQoL scores in both EP-born participants and term-born controls from the 1990s cohort, it is concerning that the positive trend in HRQoL observed in this cohort may be taking a different course in EP-born cohorts born later. From the 1980s cohort, EP-born individuals with severe disability scored numerically lower in all HRQoL domains compared to term-born controls (Paper I). However, no statistically significant results could be obtained from this small subgroup size of only six participants with severe disability, and therefore, no firm conclusion could be drawn. Interestingly, two recent studies compared cohorts born in the 1990s and 2000s, and found that children born EP in late 1990s had lower parent-reported HRQoL compared to those born EP in early 1990s (159, 160). The authors of one of these two studies also reported similar rates of neurodevelopmental impairment between the two groups (159), whereas the other study found comparable prevalence of CP, blindness, and deafness across their three birth cohorts (160). As others have previously emphasized (162, 163), EP birth should be regarded as a chronic condition, and obtaining a GA history should be a routine part of care for any patient of all age groups.

Advances in NICU care and increased parental involvement since the 1990s are also potential factors that could reduce parental stress and improve parent–child relationships, in turn benefiting long-term health of EP-born individuals (68, 164). It is intriguing to consider how our findings could align with those from a hypothetical cohort of EP-born individuals (average GA of 27 weeks) from after the 1990s, potentially showing a similar positive trend in HRQoL. Yet, this idea is purely speculative, and the true impact of such developments remains to be determined.

A further important consideration is the observed heterogeneity among EP-born participants in different studies. It is important to recognize that persons born EP exhibit significant individual variations, as reflected by wide confidence intervals. One plausible explanation for this heterogeneity is that even when two individuals share similar health conditions, their overall HRQoL can vary significantly. This discrepancy may arise from the influence of personal expectations concerning health and one's individual capacity to adapt to limitations and disabilities. These influencing factors play a pivotal role in shaping an individual's perspective on health and their overall satisfaction with life (165). Another conceivable explanation lies in the phenomenon known as the 'disability paradox', as described by Albrecht and Devlieger (166). This concept proposes that people with and those without disabilities might self-evaluate differently (166). Although not fully understood, this phenomenon is supported by a cross-sectional study from the United States, which revealed that adults with disabilities reported 4.5 out of 30 days when their physical health was not good, yet they still rated their overall health as excellent (167).

7.1.1.1 Factors associated with HRQoL in EP-born adults

Studies on EP-born adults have identified female sex as a factor associated with poorer HRQoL (9, 17). Earlier studies on the cohort showed that school-aged boys, but not girls, displayed different HRQoL outcomes compared to their term-born controls (113, 168). Sex-related outcomes were therefore explored to determine whether these findings persisted into adulthood. EP-born females scored lower, compared to EP-born males, at the age of 18 years in five domains: role emotional; mental health; self-esteem; bodily pain; and role physical. In their mid twenties, EP-born females reported higher levels of bodily pain compared to EP-born males (Paper III). This may indicate that EP-born adults are approaching the general population in terms of women reporting poorer HRQoL and mental health than men.

The influence of socio-economic factors, such as education and employment status, on HRQoL is well documented in the general population (94, 95) and has also been observed in VP/VLBW adults (13). Our study delved into these aspects and found persistent group differences that could not be solely explained by differences in education or employment status (Paper I). This finding suggests a deeper complexity, for which further investigation is warranted, particularly considering the small size of the study cohort here.

In Paper III, the influence of maternal education, used as a proxy measure for socio-economic status (SES), on HRQoL outcomes was examined. Among EP-born participants, higher maternal education was found to be associated with better scores in the domains of role emotional and role physical at the age of 18 years. However, this association was not significant in the individuals' mid twenties. This trend follows the precedent set by previous studies (107, 110, 112, 158, 160), whereby maternal education was reported to affect the outcomes of EP-born individuals by some studies (158, 160), whereas others found no such association (107, 110, 112). However, in the context of Norway's healthcare system, which offers free access to all, the study results presented here did not indicate significant disparities in SES in relation to HRQoL. This observation thus leads to speculation of the potential mitigating effect of universal healthcare access on the HRQoL among EP-born individuals.

7.1.1.2 Neonatal factors influencing HRQoL in EP-born adults

Research on the influence of neonatal factors on the HRQoL of adults born EP is relatively scarce. This could be due to an assumption that the impact of neonatal factors on the HRQoL diminishes as individuals age. Despite this, recognizing the importance of neonatal factors in relation to the HRQoL is crucial for early identification of individuals at high risk of poor HRQoL and who thus may face associated long-term sequelae.

In the study presented in Paper I, no statistically significant differences in HRQoL outcomes were found between EP-born participants with and those without BPD. This finding contrasts with results from a Swedish study of preterm births in the 1990s, which showed reduced general health and vitality in the BPD group compared to controls (169). Additionally, the research work presented in Paper III showed that postnatal steroid treatment was associated with poorer HRQoL in both 1980s and 1990s cohorts, confirming previous findings for the 1990s cohort at the age of 10 years (168). The consistency of these results raises the question of ‘bias by indication’, considering that postnatal steroid treatment was primarily administered to the most severely ill neonates. The findings about steroid use after birth are important and correlate with what is already known from previous studies. They also fit with our understanding of how postnatal steroid treatment is used for the most severely ill. Moreover, the results presented here echo the findings of a systematic review from the early 2000s, which highlighted the dramatic increases in neuro-developmental impairment associated with postnatal steroid treatment (170). Therefore, while the study results here are significant, they are not entirely surprising, considering the historical context and evolving understanding of the impact of postnatal steroid treatment.

In light of these observations, the role of neonatal interventions, such as postnatal steroid treatment, in shaping long-term HRQoL outcomes in EP-born adults warrants closer examination. While the study findings presented here align with previous research, highlighting the nuanced impact of early medical decisions, they also underscore the challenges of isolating the effects of specific neonatal factors on HRQoL due to sample size limitations. This emphasizes the need for larger, more comprehensive studies to better understand these relationships and guide interventions that support optimal development and quality of life in EP-born individuals.

7.1.1.3 Longitudinal development

EP-born participants demonstrated poorer HRQoL, compared to term-born controls, at the age of 24 years and this trend persisted unchanged at the age of 34 years (Paper I). This finding aligns with results from other studies. A study of VLBW individuals, which notably also used the SF-36 questionnaire for its assessments, found that HRQoL declined from the age of 20 to 32 years but remained stable in the term-born control group (18). A previous study using HUI3 found ELBW individuals reported poorer HRQoL from adolescence to their mid thirties, compared to controls (15). Another study, which also used HUI3 to assess VLBW individuals from the ages of 19 to 28 years, while lacking a control group, found lower scores in psychological domains as measured by the WHO quality of life instrument (99). These findings underscore the need for support and interventions aimed at improving HRQoL for EP-born individuals as they transition from young to mid adulthood.

7.1.1.4 Cohort differences

Comparison of the two EP-born cohorts (i.e. 1980s vs 1990s; Paper III) found only minor differences between them, with, at best, a tendency towards better outcomes in the 1990s cohort. However, a clear link between HRQoL and neonatal factors was not established, except for the influence of postnatal steroid treatment, which may be subject to bias by indication. In practical terms, these findings suggest that the impact of neonatal medicine and care on HRQoL could be less significant than expected.

7.1.2 Mental health in EP-born adults

The studies presented in this thesis found that EP-born adults reported more mental health problems than term-born controls, especially internalizing problems such as anxiety and withdrawal. As discussed in Paper II, these findings are in line with two meta-analyses, which found higher rates of depression and anxiety in young VLBW or ELBW adults (126, 171). Additionally, a qualitative study from Germany described mental health sequelae in all EP-born participants aged over 40 years, with half of the EP-born group reporting that EP birth had an influence on their mental health (115). This suggests the importance of follow-up after EP birth into adulthood, as some consequences of EP birth may become apparent only after young adulthood.

It is important to recognize that studies assessing mental health through self-reported questionnaires, including the studies presented in this thesis, often yield higher scores (indicating worse outcomes), compared to evaluations performed by psychiatrists by using diagnostic criteria from DSM-IV and ICD-10 for psychiatric disorders (172). Despite these higher scores among the EP-born group relative to term-born controls, variability within the EP-born group itself should not be overlooked. This variability suggests that while, on average, EP-born individuals may report more mental health problems, some have mental health outcomes comparable to those of the term-born control group. Therefore, healthcare providers should offer individual examination to EP-born individuals, rather than assume that they are simply part of the general population.

7.1.2.1 Factors associated with mental health in EP-born adults

In the studies presented in this thesis, after adjusting for sex, no statistically significant differences in mental health outcomes were obtained among participants, contrasting with the overall trend observed in the general population and in a study of VLBW participants from the United States which found women to be more susceptible to internalizing problems (125, 173, 174). The study findings in this thesis challenge reports from the existing literature, warranting further investigation.

Recent studies have provided intriguing insights into the social dynamics of individuals born VP, often reporting lower scores in terms of friendships and social relationships compared to full term-born peers (55). This trend was also observed in the research work described in this thesis among the EP-born 1980s cohort, with these participants reporting fewer relationships compared to term-born controls. In contrast, a study of a 1990s preterm-born adult cohort from Australia presented a different picture. The majority of these participants expressed satisfaction with their social relationships (175).

This variation across different birth cohorts and geographical regions raises interesting questions about factors influencing social satisfaction among preterm-born individuals. The quality of social relationships is known to have a significant impact on mental health. Therefore, the contrasting findings across studies suggest that the relationship between preterm birth and later social satisfaction might not be straightforward and could be influenced by a range of environmental, cultural, and healthcare-related factors. Understanding these nuances is crucial, as it can guide interventions and support mechanisms to improve mental health outcomes of individuals born preterm.

Furthermore, the studies presented in this thesis found that EP-born participants had higher rates of unemployment or were more likely to receive disability benefits compared to term-born controls. Employment has been linked with lower odds of developing lifetime anxiety (173), highlighting the importance of socio-economic factors in determining mental health outcomes for preterm-born individuals.

Additionally, mental health problems can also manifest as discomfort and fatigue. A recent study investigated the associations between mental health and pain and tiredness in adults born VP by incorporating individual participant data from six cohorts (176). The authors found that elevated levels of internalizing, externalizing, and overall problems on mental health scales were associated with heightened levels of pain and fatigue in both preterm- and term-born groups (176). Another study highlighted a link between mental health and exposure to maternal mood and anxiety disorders among ELBW participants (133).

Physiological factors in relation to mental health have also been examined. For example, a study suggested a link between adverse mental health outcomes and changes in brain anatomy such as reduced local gyrification index (132). Furthermore, ELBW individuals with elevated afternoon cortisol levels were found to report a higher prevalence of internalizing problems compared to those with lower cortisol levels (134). Existing research on the impact of EP birth on mental health is limited. More studies are crucial to gain better understanding of this complex interplay of different factors on mental health in the context of EP birth, and to aid in developing prevention and treatment strategies.

In conclusion, while the links between preterm birth, mental health, social dynamics, and physiological factors are compelling, they are far from being fully understood. While existing research provides valuable insights, it also highlights the complexity of these relationships and the need for more comprehensive studies to deepen our understanding.

7.1.2.2 Longitudinal development

In the study presented in Paper II, an increase in mental health problems was observed over time among EP-born participants from the 1990s cohort. Specifically, heightened scores were noted on internalizing problems, the syndrome scale for anxious/depressed feelings, somatic complaints, and attention problems in this group. The EP-born participants were also found to score poorer in the HRQoL mental health domains compared to term-born controls, as described in Paper I.

Comparatively, only two longitudinal studies—one from Norway and the other from Canada—have examined mental health trajectories of preterm-born individuals, with both including participants based on BW (VLBW, i.e. <1500 g). Both studies reported an increase in the prevalence of internalizing problems among their participants (100, 177), which are aligned with results presented in this thesis. Additionally, a third study highlighted that VP/VLBW individuals exhibited significantly more attention problems and poorer attention span, compared to term-born controls, persisting from childhood into adulthood (178). Contrasting with this, a fourth study found no significant differences of anxiety or mood disorders between

EP/ELBW subjects and term-born controls as the study participants progressed from the ages of 18 to 26 years (131).

In conclusion, research findings presented in this thesis add to the growing body of evidence indicating a worsening trend in mental health outcomes over time among EP-born individuals, paralleling findings from international studies on VLBW participants. This consistency across different cohorts and countries of study highlights the importance of monitoring and supporting the mental health of preterm-born individuals throughout their lives.

7.1.3 Subjective health complaints in EP-born adults

Research findings presented in Paper I provide an optimistic perspective on the trajectory of subjective health complaints among adults born EP. Contrary to the expectations set by previous research, which underscored the value of subjective health complaints in capturing personal burdens and signalling potential mental health issues (136), the study discussed in Paper I observed a decline in subjective health complaints as participants aged from 24 to 34 years. This finding is encouraging, especially when contrasted with an earlier study that indicated an increase in psychological health complaints among healthy EP-born individuals transitioning from adolescence to young adulthood (16).

Furthermore, it's possible that the EP-born participants have under adaptation over time, leading to altered perceptions of their health complaints. This suggests that their responses to measures of subjective health complaints could vary over time, a phenomenon discussed in Paper I. These changes in perception might be attributed to a ‘response shift’, a concept introduced by Sprangers and Schwartz (179). A response shift occurs when there is a change in an individual’s self-evaluation due to adjustments in internal standards, values, or conceptualization of HRQoL (179). This dynamic underscores the complexity involved in assessing subjective health over time and highlights the potential for positive adaptation in the face of early life challenges.

7.2 Methodological considerations

7.2.1 Study design

By applying a longitudinal approach to population-based cohorts, the study design described in this thesis is well suited for exploring the development of HRQoL among adults born EP (152).

7.2.1.1 Bias

All mothers included in the study were residents of a well-defined geographical area, and the study initially achieved a high inclusion rate. Moreover, as all children had free access to healthcare, thus mitigating the risk of bias related to socio-economic factors, the study population can be considered relatively representative and unbiased for survivors of EP birth. Concerning the control groups, the selection criteria involved choosing the temporally nearest term-born child of the same sex, with a BW ranging from 3 to 4 kg (these weights fell within the 10th to 90th percentile for all births in Norway during the specified time period) (180). Using this approach aimed to minimize the risk of selection bias. These criteria were consistently applied throughout the entire study period.

Non-responders are common and represent a challenge in longitudinal studies, as they can introduce bias (152). Various types of bias can occur; for instance, non-responders may have reasons for not participating that are related to the variables being studied, or they may systematically differ from responders (152). To mitigate the risk of these biases, minimizing participation decline was given high priority. Study participants were given great flexibility. For example, in some cases, participants were allowed to complete questionnaires at their home or examinations were arranged to take place closer to their home, especially for those who had to travel long distances. Additionally, a comparative analysis of characteristics between participants and non-participants was performed, as detailed in Papers I and II, with the aim to assess for potential response bias. As a result, no significant differences were found between those who actively participated and non-participants (for details, see Appendix VI and Paper II).

In the study presented in Paper III, the issue of missing values was addressed by imputation, a method that helps to maintain data set integrity. In the imputation model, variables were carefully selected that were considered potential predictors of missingness or influential in determining the likelihood of a value being missing. These included age, sex, cohort, HRQoL scores, use of postnatal steroids, and maternal education. This approach aimed to create a more robust and representative data set by incorporating these key variables, thereby reducing bias and enhancing the accuracy of study analysis. However, it is important to acknowledge that imputation, while mitigating the effects of missing data, relies on assumptions about the nature of the missingness and may introduce its own form of bias. Therefore, results derived from imputed data should be interpreted with an understanding of these underlying assumptions and potential limitations.

The use of questionnaires introduces several potential biases in the response patterns. There is uncertainty regarding whether respondents have accurately understood the questions or whether their motivation has influenced their answers. Some participants may attempt to present themselves in a favourable light, whereas others might complete the questionnaire hastily. A critical aspect to consider is the cognitive demands placed on respondents, who are required to fully understand the questions. Unfortunately, the extent of participants' comprehension of the questions cannot be definitively determined. Use of validated questionnaires (119, 181, 182) is a strength of the study approach described in this thesis.

7.2.2 Reliability and validity of measurements

Evaluating reliability involves establishing that a scale or measurement produces results that are both consistent and replicable (78). Further, evaluating validity involves assessing to which extent an instrument measures what it is intended to measure (152).

For the purpose of the research presented in this thesis, we utilized the CHQ-CF87, SF-36, YSR, ASR, and HBSC-SCL questionnaires, all of which have been validated. Previous research also used the SF-36 (100, 116) and ASR (126, 183) to evaluate HRQoL and mental health in the preterm-born population.

7.2.2.1 HRQoL measurements (CHQ-CF87 and SF-36)

The CHQ-CF87 was one of the few generic measures developed for children at the time the research work presented here was planned. It has been demonstrated to have good reliability and psychometric properties (141, 142), and also shown to have high sensitivity in detecting changes related to preterm birth (184).

The SF-36 questionnaire has been shown to have good reliability (144). Good internal consistency has been found among the Norwegian population with use of the SF-36 (90). Furthermore, a rationale for selecting the SF-36 is that it is considered to be the adult counterpart of the child questionnaire CHQ-CF87, with the latter used up to the age of 18 years (185).

Ceiling effects (i.e. maximum scores) for the role scales were previously reported in the general population (90). In the study here, scores close to the ceiling were found for physical functioning among term-born controls (Table 7), which might have caused an overestimation of group differences.

For HRQoL scales, changes are subjective, and therefore a matter of opinion. However, many investigators in this field regard changes of between 5% and 10% (or of 5–10 points on a 100-point scale) as meaningful (78). These values have guided interpretation for the research presented in this thesis.

As described earlier in Section 3.2, there is a lack of consensus on the definitions of HRQoL and QoL. This ambiguity complicates the determination of what constitutes the most accurate assessment. To enhance clarity, researchers should explicitly state what they have measured in their studies. For the research presented here, HRQoL was measured with use of the SF-36, and referred to as HRQoL measures (143).

Some studies of ELBW and VP populations utilize the HUI3 (13–15). This set of utility instruments, developed from economics and decision theory, evaluates performance across eight health status attributes—vision, hearing, speech, ambulation, dexterity, emotion, cognition, self-care, and pain—aiming to estimate individual patients’ overall preferences for various health statuses (186). A study comparing the HUI3 and the SF-6D (a shorter version of the SF-36) revealed a discordance between the two measures in a sample comprising VP/VLBW adults and a control group (187). Therefore, caution is warranted when comparing results from the two measures, as they do not align perfectly.

In the study here, generic questionnaires were chosen to investigate similarities and differences in HRQoL between EP-born adults and their term-born controls. At present, a dedicated HRQoL questionnaire exclusively tailored for individuals born preterm is lacking, in contrast to existing questionnaires designed for other patient cohorts such as those with heart conditions (188) and asthma (189). Meanwhile, general HRQoL and mental health measurements were included in a recent recommendation article exploring common core assessments in follow-up studies of adults born preterm (146). The consideration of whether to develop a distinct questionnaire for the preterm-born population is a matter that requires careful evaluation. The rationale behind this perspective lies in the notable diversity within the preterm-born group, which distinguishes it from other patient populations. Unlike diseases where symptoms can often be categorized or associated with a specific medical condition, such characterization is not possible within the preterm-born group. Therefore, the development of a specialized HRQoL questionnaire potentially should involve a collaborative process, incorporating insights from healthcare professionals, researchers, and preterm-born individuals themselves, to ensure that the tool is both inclusive and reflective of their experiences. The positive aspect of choosing a generic questionnaire is that the preterm-born population can be compared with the general population and with other disease groups for whom generic tools have also been used.

7.2.2.2 Mental health measurement (YSR and ASR)

The YSR and ASR questionnaires have been demonstrated to have good reliability, with test–retest results showing scores ranging from the 0.83 to 0.85 for most scales, and none falling below 0.71, thus demonstrating robust consistency (119, 182). The average Cronbach’s alpha for the ASR stood at 0.83, indicating good internal consistency, and for the scales, it was even higher at 0.85 (119, 190).

Further reinforcing the utility of these measures, scores on the Young Adult Self-Report (now ASR) scale have been linked with significant predictive correlations in longitudinal studies, indicating high reliability (191). For instance, a Dutch study observed considerable stability in problem behaviours over a 10-year follow-up period by using the YSR followed by the Young Adult Self-Report (now ASR) (148). The consistency of these tools over time bolsters their applicability in longitudinal research, allowing for a more nuanced understanding of developmental trajectories in mental health.

Concerning interpretation of the mental health measurement, the clinical range can be described by converting raw scores to norm-based T-scores. However, it is recommended in a research setting to use raw scores and report mean differences (119): this approach was applied in the research presented here.

Currently, no literature exists on validation of the ASR in the Norwegian population. The questionnaire was translated into Norwegian and back into English by experts at the Regional Centre for Child and Adolescent Mental Health in Oslo, informed by the questionnaire developers. Still, there are no details of its validation process in Norway, highlighting a significant gap. This lack of validation data for Norwegian adults underscores the need for future validation studies.

However, the ASR has been validated for use in adult populations in several other countries, for instance the United States, Iceland, and Italy (119). It has also been utilized in research involving preterm-born populations in Canada (174, 177), Finland, Germany, the United States (126), and Norway (100, 183). This widespread international use suggests its potential applicability.

7.2.2.3 Health complaints measure (HBSC-SCL)

The HBSC-SCL is designed for children and adolescents, with a primary focus on the 11- to 15-year age group (192). The questionnaire is tailored to reflect accurately the health experiences and understanding levels of this relatively young population. Consequently, its direct application to adults may not be ideal. The validity and reliability of the HBSC-SCL have been established specifically for a younger audience. When applied to an adult population, these psychometric properties may not be as effective due to potential differences in how adults interpret questions and their varied thresholds for reporting symptoms. However, the HBSC-SCL covers a range of subjective health complaints, including somatic symptoms such as abdominal pain, headaches, and back pain, as well as psychological symptoms such as feelings of low mood, nervousness, and sleep difficulties. These problems are also commonly experienced by adults, making these aspects of the questionnaire relevant across ages. Additionally, in the context of the research presented in this thesis, the longitudinal nature of the HBSC-CL has enabled tracking and analysis of health trends over time, offering valuable insights that could be extrapolated to understand similar trends in adult populations.

The three instruments used in this study complement one another. The HRQoL provides a general overview, whereas the mental health instrument delves more deeply into specific symptoms such as anxiety and internalizing behaviours. Furthermore, the instrument for evaluating subjective health complaints addresses more detailed aspects of health concerns. To conclude, well-established questionnaires, with high validity and reliability for evaluating both HRQoL and mental health problems, were used in this study. However, it is important to approach the findings regarding subjective health complaints with caution, especially considering that these measures are not validated for adult populations.

7.2.3 Statistical considerations

7.2.3.1 Study power

As the research work described in this thesis was part of a larger study, the power calculation was based on lung function outcomes, specifically by measuring FEV_1 differences (140). Consequently, a sample size could not be explicitly calculated that would mitigate the risk of type II errors, which occur when a real effect or difference between groups is not detected, even when it exists (i.e. failure to reject the null hypothesis). While acknowledging this as a limitation, efforts were therefore focused on recruiting as many participants as possible within the frames of the study, to minimize the impact of this limitation.

In the study reported in Paper III, multiple imputation, specifically MICE (155), was used to reduce bias caused by missing data. Multiple imputation is currently regarded as the optimal method for handling missing data (152). It is important to note that multiple imputation may yield biased results if variables are missing not at random. (193).

7.2.3.2 Adjustments

The complexity of neonatal intensive care involves numerous factors, both known and unknown. These factors, including the cause of EP birth (194), may have impacted the exposure and/or the outcomes discussed in this thesis. Here, guidance was taken from existing reviews and cohort studies on EP birth, as well as from our own previous research to find potential confounders, and subsequent adjustments made. Confounding occurs when an external variable influences both the exposer variable and the outcome variable of interest (152)—in the research presented in this thesis, between EP birth (exposer variable) and questionnaire results (outcome variables).

Controls were matched by birth year and sex to minimize confounding by these factors. However, studies presented in Papers I–III adjusted for sex, as it was a central part of the findings on the 1991–2 cohort in previous publications (113, 168, 195). Sex can be a predictor for HRQoL outcomes, and one of the research objectives was to investigate whether there were variations within and between groups that influenced the outcome based on sex.

As described in Paper I, the study adjusted for education and employment status, both factors that occurred after being born. This adjustment introduced potential ambiguity, as these factors could be outcomes directly linked with EP birth or be merely incidental occurrences. Thus, the appropriateness of this adjustment warrants discussion. Previous studies in the general population have indicated that employment status can impact HRQoL (196). One objective was to find out whether this holds true for the EP-born population.

In the study presented in Paper III, the predictive effect of SES was estimated, as measured by maternal education, following the findings of other comparable studies. These studies adjusted for SES in the context of EP birth (159, 160, 197) and HRQoL (198, 199), and identified SES as a risk factor for preterm birth (200). In the study here, maternal education was measured at the first follow-up of participants. Education represents a lifelong exposer that is relevant not only to the actual educational achievement at the time of birth of the preterm-born individual. However, a majority of previous studies have measured education at the time of birth (201). In conclusion having more comprehensive information on SES such as total parental income or education at the time of birth would have been beneficial.

Finally, in the study reported in Paper III, the predictive effect of postnatal steroid treatment was evaluated. In an earlier publication by the research group on the 1991–2 cohort, poorer role/social functioning at the age of 10 years was reported in those who had received postnatal steroid treatment (168).

In summary, to the best of our knowledge, we adjusted for the important factors that are known to influence the outcomes of the research presented here. However, we cannot exclude the possibility that there are other factors, not accounted for in our analysis, which might have influenced the results, which, in turn, highlights the potential for oversight in capturing all variables that could impact the findings. Therefore, while our adjustments were thorough based on current understanding, future research should aim to identify and include any factors that could be potentially overlooked, to ensure a more comprehensive understanding of the influences at play.

7.2.4 External validity

External validity refers to the extent to which the findings or associations observed in a study hold true across variations in individuals or contexts—in other words, whether the concept relates to the generalizability of the findings (152).

A limitation of the research presented in this thesis is the small number of participants in each cohort, which raises concerns about the generalizability of the study findings. Caution therefore is warranted when interpreting subgroup analyses.

Study controls were selected to represent the broader population. When compared to norm-based data from the Norwegian population, participants born at term displayed comparable scores across all eight domains of the SF-36 at the age of 34 years (see Section 6.4, Table 6). Additionally, mental health scores of term-born controls aligned closely with normative data (see Section 6.4, Table 8). However, marginally higher scores for bodily pain and general health were reported by term-born controls at the age of 27 years (see Section 6.4, Table 7). In sum, term-born controls overall seemed to represent the general population. This bolsters the reliability of the study findings, namely significant differences in HRQoL and mental health outcomes between preterm-born individuals and their term-born counterparts.

The study findings here can be generalized to similar populations of EP-born adults from the 1982–5 and 1991–2 cohorts. The question arises as to whether the findings on cohorts born in the 1980s and 1990s are still relevant to children born in more recent years. A study comparing data from the 1980s to those from 1997 showed that increased survival rates at EP birth led to higher incidences of morbidity upon hospital discharge, with BPD being particularly prominent (202). Advances in neonatal care now enable survival of infants born at increasingly lower GA. This suggests that groups of individuals born EP in recent times include those with lower GA compared to EP-born participants in the research presented in this thesis. It is not unlikely that this also could influence long-term outcomes. For instance, a study from Sweden found that a majority of children born before 24 weeks' GA suffered from neurodevelopmental disorders (203). The long-term effects of advances in neonatal care on HRQoL and mental health are still unclear. Consequently, it remains uncertain whether the results presented in this thesis can be generalized to EP-born infants born in the current era. Nonetheless, these study findings are important, as they imply that survival rates of EP-born infants could significantly impact HRQoL and mental health of future generations.

7.3 Clinical implications

The research presented in this thesis aims to share important insights into HRQoL and mental health in EP-born adults with the public. Significant resources are allocated to neonatal intensive care, and yet the long-term consequences of birth in the second trimester remain inadequately understood. The study findings discussed in this thesis add to what is known about HRQoL and mental health in EP-born adults, and should be shared with primary healthcare services, schools, and, last but not least, the preterm-born individuals themselves. Many preterm-born individuals wonder if others share similar experiences, as discussed in Kine Albringsten's podcast in 2021 about living with invisible diseases (204).

The study results discussed in this thesis significantly contribute to our understanding of the development of HRQoL, subjective health complaints, and mental health in today's EP-born adult population. Despite the small cohort size and the fact that the study participants might not be fully representative of today's EP-born individuals with respect to characteristics, the findings presented here are nevertheless important. Both catch-up trends and persistent differences in the EP-born group compared to their term-born controls were observed. Given that these individuals are only in their mid twenties and thirties, they have a significant lifetime ahead of them. Therefore, it is the responsibility of the wide research community to continue investigating the long-term outcomes for these adults. The research presented here not only sheds light on the current health status of EP-born individuals, but also sets the stage for future research to monitor and support their health as they age.

The results presented in this thesis suggest that both HRQoL and mental health are affected in EP-born individuals, with symptoms often manifesting in adulthood. A meta-analysis of VLBW adults also found an elevated risk of internalizing problems in this group (118). This suggests that individuals born EP would benefit from being routinely followed up by the healthcare system into adulthood. This viewpoint is also supported by preterm-born adults themselves (205). Currently, the Norwegian guideline recommends monitoring of EP-born children until the age of 5 years (206), although this guideline is currently under revision.

In summary, while recognizing the challenges faced by the oldest preterm-born individuals, HRQoL and mental health assessments should be integrated into standard clinical practice for this specific population. Healthcare professionals should be well educated on HRQoL and mental health assessments, including their application and interpretation. Further, this underscores the importance for healthcare professionals to consider discussing HRQoL and mental health in their interactions with adults born EP.

7.4 Future perspectives

The preterm-born individuals, born in the early 1980s, who took part in the studies presented in this thesis represent a ‘pioneer generation’ in the sense that during the preceding decades, most infants born at such an early gestational stage did not survive. Currently, a growing number of survivors of extreme prematurity are approaching adulthood. This evolving landscape underscores the importance of ongoing research in this domain to better understand and address the unique healthcare needs of this population.

The study findings presented in this thesis indicate that both HRQoL and mental health outcomes are poorer in the EP-born group compared to term-born controls. More studies are needed to investigate the potential causes and consequences of these differences. Two research articles, published in 2020 and 2021, respectively, identified priority areas of research in preterm-born populations, both including measurements of HRQoL and mental health outcomes (146, 207). Efforts should be focused on establishing a consensus for a uniform methodology to measure self-reported mental health outcomes and HRQoL in the EP-born population. This process should include validation studies on use of relevant questionnaires in the EP-born group. If the same questionnaires are used across different countries, comparisons can be made easily as a result, which will enhance the power and generalizability of research on the EP-born population.

The measure of HRQoL serves as a crucial health indicator, and gaining insights into the challenges faced by EP-born adults is valuable not only for the individuals themselves, but also for healthcare providers and policymakers. Intervention studies, for example, evaluating the impact of physical activities on enhancing outcomes in EP-born participants—particularly in areas such as HRQoL and mental health—could be a key step in improving healthcare for, as well as in follow-up of, this group.

8. Conclusions

In accordance with the specific study aims and research questions (see Section 4), the main study conclusions are summarized below.

- **HRQoL**
    - EP-born participants from the 1980s cohort, at the age of 34 years, showed poorer self-reported HRQoL compared to term-born controls, particularly in mental health domains (Paper I).
    - Although no firm conclusions could be derived due to the small number of EP-born individuals with severe disabilities, this subject group was found to score consistently lower in all HRQoL domains compared to their EP-born counterparts with no severe disabilities (Paper I).
    - Similar self-reported HRQoL were found between EP-born participants from the 1990s cohort and their term-born controls (Paper II).
- **Subjective health complaints**
    - EP-born adults from the 1980s cohort who were considered healthy reported more subjective health complaints, particularly psychological complaints, compared to their term-born controls, at the age of 34 years (Paper I).
- **Mental health**
    - EP-born adults from the 1990s cohort reported more mental health problems, particularly internalizing problems and specific symptoms on the syndrome scales of anxiety/depression and withdrawal, compared to term-born controls (Paper II).
- **Longitudinal development**
    - EP-born participants reported poorer HRQoL, compared to term-born controls, and this trend remained unchanged across the age span from 24 to 34 years (Paper I).
    - A positive development (i.e. lower scores) with respect to sub-scores for psychological subjective health complaints was observed among EP-born participants from the age of 24 to 34 years, compared to term-born controls (Paper I).

  - The rate of self-reported mental health problems increased from the age of 18 to 27 years among EP-born adults from the 1990s cohort, which was higher than in term-born controls (Paper II).
- **Cohort differences**
  - No statistically significant differences in self-reported HRQoL were found between adults of similar ages who were born EP in two distinct eras—the 1980s versus the 1990s. Nevertheless, in their mid twenties, EP-born individuals from the 1980s cohort displayed a trend towards poorer HRQoL compared to their corresponding counterparts from the 1990s cohort (Paper III).

Table 3 Studies on self-reported health-related quality of life in EP/ELBW or VP/VLBW adults in order of birth years of study participants[*]

Study[**]	**Country**	**Study design**	**BW (g), GA (wk)**	**Control group**	**Birth year**	**Age**	**Measurement**	**Outcome in EP-born vs term-born**
Perez et al., 2020 (115)	Germany	Qualitative study	<33 wk or <1500 g	No	1964–98	>20	Interview	High prevalence of self-reported sequelae, indicating *poorer physical (65%) and mental (45%) health outcomes*
Van der Pal et al., 2020 (9)	11 countries	Review	<1500 g, <32 wk	Yes	1971–92	18–36	SF-36, HUI2, HUI3, CHQ, CHIP-AE, 15-D, questionnaire from the theories of Aggernæs, visual analogue scale ranging from 0 to 100	*No conclusive evidence of HRQoL difference*
Bolbocean et al., 2023 (17)	6 countries	Meta-analysis	<32 wk or <1500 g	Yes	1985–95	18–28	HUI3, SF-12, SF-36	*Poorer HUI3 scores, no differences in SF-6D*
Bjerager et al., 1995 (104)[a]	Denmark	Cohort study	<1500 g	Yes, >2500 g	1971–4	18–20	Questionnaire from the theories of Aggernæs	*No difference in VLBW free of disability*, but *VLBW with disability* had *lower* objective and subjective *QoL*
Björkqvist et al., 2018 (105)[a]	Finland	Cohort study	<1500 g	Yes	1971–4	18–27	15-D	*No difference*

Table 3 *(continued)*

Study**	**Country**	**Study design**	**BW (g), GA (wk)**	**Control group**	**Birth year**	**Age**	**Measurement**	**Outcome in EP-born vs term-born**
Hertz et al., 2013 (106)	Denmark	Cohort study	<32 wk	Yes	1974–6, 1980–2	24–26 30–32	SF-12	*No difference*
Hack et al., 2007 (107)[a]	Canada	Cohort study	<1500 g	Yes	1977–9	20	CHIP-AE	*No difference*
Saigal et al., 2006 (101)[a]	Canada	Cohort study	<1000 g	Yes	1977–82	23.3	HUI2	*No difference*
Poole et al., 2017 (102)[a,b]	Canada	Cohort study	<1000 g	Yes	1977–82	22–26	SF-36	*No difference*
Dinesen & Griesen, 2001 (108)[a]	Denmark	Cohort study	<1500 g	Yes	1980–2	18	Questionnaire from the theories of Aggernæs	*Poorer objective QoL* and *similar subjective QoL*
Cooke et al., 2004 (109)[a]	UK	Cohort study	<1500 g	Yes	1980–3	19–22	SF-36	*No difference*, but lower for preterm-born, compared to controls, in physical functioning and general health perception score

Table 3 *(continued)*

Study[**]	**Country**	**Study design**	**BW (g), GA (wk)**	**Control group**	**Birth year**	**Age**	**Measurement**	**Outcome in EP-born vs term-born**
Båtsvik et al., 2015 (16)[a]	Norway	Cohort study	<28 wk, <1000 g	Yes	1982–5	17, 24	SF-36	*Poorer psychological HRQoL*, at 24 years
Verrips et al., 2012 (110)	Netherlands	Cohort study	<32 wk, <1500 g	No	1983	14, 19	HUI3	*No term control group* *HRQoL stable* from adolescence to young adulthood
Van Lunenburg et al., 2013 (99)[c]	Netherlands	Cohort study	<32 wk, <1500 g	No	1983	19, 28	HUI3	*No term control group* *No change in HRQoL* from 19 to 28 years
Natalucci et al., 2013 (103)[a]	Switzerland	Cohort study	<1000 g	Community norms	1983–5	23.3	SF-36	*Poorer mental health*, but better physical health
Saigal et al., 2016 (15)[a,b]	Canada	Cohort study	<1000 g	Yes	1985–6	12–16, 22–26, 29–36	HUI3	*Poorer HRQoL*, from early teens to mid thirties
Baumann et al., 2016 (13)[a]	Germany	Cohort study	<32 wk, <1500 g	Yes	1985–6	13, 26	HUI3	*Poorer HRQoL*

Table 3 *(continued)*

Study[**]	**Country**	**Study design**	**BW (g), GA (wk)**	**Control group**	**Birth year**	**Age**	**Measurement**	**Outcome in EP-born vs term-born**
Hallin & Stjernqvist, 2011 (98)[a]	Sweden	Cohort study	<29 wk	Yes	1985–1986	18	Visual analogue scale ranging from 0 to 100	*No difference*
Darlow et al., 2013 (111)[a]	New Zealand	Cohort study	<1500 g	Yes	1986	22–23	SF-36	*No difference*
Lund et al., 2012 (208)[a]	Norway	Cohort study	<1500 g	Yes	1986–8	20	SF-36	*Poorer HRQoL* in mental health domains
Husby et al., 2016 (100)[a,d]	Norway	Cohort study	<1500 g	Yes	1986–8	20, 23	SF-36	*Poorer HRQoL*, declining from 20 to 23 years
Wollum et al., 2022 (209)[c]	Norway	Cohort study	<1500 g	Yes	1986–8	26, 28	HADS, SF-36	*Poorer general functioning and mental health-related quality of life*
Berdal et al., 2022 (18)[c]	Norway	Cohort study	<1500 g	Yes	1986–8	20, 23, 32	SF-36	*Lower HRQoL*
Gäddlin et al., 2009 (112)[a]	Sweden	Cohort study	<1500 g	Yes	1987–8	20	SF-36	*No difference*
Girard-Bock et al., 2021 (116)	Canada	Cross-sectional observational study	<30 wk	Yes	1987–96	19–29	SF-36v2 and in-depth questionnaire	*No difference*; however, VP reported their health was poorer than the general population

Table 3 *(continued)*

Study**	**Country**	**Study design**	**BW (g), GA (wk)**	**Control group**	**Birth year**	**Age**	**Measurement**	**Outcome in EP-born vs term-born**
Roberts et al., 2013 (14)[a]	Australia	Cohort study	<28 wk or <1000 g	Yes	1991–2	18	HUI3, SF-36	*No difference*
Vederhus et al., 2015 (113)[a]	Norway	Cohort study	<28 wk, <1000 g	Yes	1991–2	18	CHQ	*No difference*
Selman et al., 2023 (114)[e]	Australia	Cohort study	<28 wk or <1000 g	Yes	1991–2	18, 25	HUI3	*Poorer HRQoL*
Ni et al., 2021 (161)	United Kingdom and Ireland	Cohort study	<26 wk	Yes	1995	19	HUI3	*Poorer HRQoL*

[*] Overview of studies on HRQoL comparing between EP/ELBW or VP/VLBW adults and term-born controls.

[**] The studies listed in the table were identified by using a search strategy on Medline, Embase, CINAHL, or APA PsycINFO, including the following search words: ‘infant, very low birth weight’, ‘infant, extremely low birth weight’ OR ‘infant, extremely premature’ OR ‘preterm’, ‘premature’, ‘very-low’, ‘very low’, ‘extremely-low’, ‘extremely low’, ‘birth-weight’ or ‘birth weight’ or ‘birthweight’ or ‘born or infant*’ or ‘child*’ or ‘adult’AND ‘quality of life’, ‘quality of life’ or ‘HRQOL’ or ‘QoL’ or ‘SF-36’ or ‘SF36’ or ‘short form 36’ or ‘SF-12’ or ‘SF12’ or ‘short form 12’ or ‘HUI’ or ‘Health Utilities Index’AND ‘Adult’ or ‘adult*’ or ‘18 year*’ or ‘age* 18’. The references list of included papers were reviewed.

[a] Included in the review by Van der Pal et al., 2020 (9).

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[b] The same cohort as in Saigal et al., 2006 (101).

[c] The same cohort as in Verrips et al., 2012 (110).

[d] The same cohort as in Lund et al., 2012 (208).

[e] The same cohort as in Roberts et al., 2013 (14).

Abbreviations: 15-D, Quality of life questionnaire; BW, birthweight; CHIP-AE, Child Health and Illness Profile—Adolescent Edition; CHQ, Child Health Questionnaire; ELBW, extremely low birthweight; EP, extremely preterm; GA, gestational age; HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; HUI3, Health Utilities Index Mark 3; SF-12, Short Form 12; SF-36, Short Form 36; VLBW, very low birthweight; VP, very preterm; wk, week; y, year.

Table 4 Studies on self-reported mental health in EP/ELBW or VP/VLBW adults in order of birth years of study participants[*]

Study[**]	Country	Study design	BW (g), GA (wk)	Control group	Birth year	Age	Measurement	Outcome in preterm-born vs term-born
Tideman et al., 2001 (210)	Sweden	Cohort study	<35 wk	Yes	1976–7	19	SCL-90	*No significant differences* in self-reported mental health
Pyhälä et al., 2017 (126)	Canada, Finland, Norway, USA	Meta-analysis	<32 wk, <1500 g	Yes	1977–89	19–29	YASR, ASR	*High risk of internalizing problems* and lower risk of externalizing problems
Mathewson et al., 2017 (171)[a]	Canada, Switzerland	Systematic review and meta-analysis	<29 wk, <1000 g	Yes	1977–85	22–36	YASR, RSES, STAI, ADHD-RD, BSI, SSS, CSES, MINI	*More internalizing problems* and higher risk of self-reported anxiety problems
Hack et al., 2004 (174)[b]	USA	Cohort study	<1500 g	Yes	1977–9	20	YARS	*More mental health problems*
Boyle et al., 2011 (211)[b,c]	Canada	Cohort study	<1000 g	Yes	1977–82	22–26	YARS	*More internalizing problems*
Van Lieshout et al., 2018 (177)	Canada	Cohort study	<1000 g	Yes	1977–82	12–16, 22–26, 30–35	OCHS-R, YARS	*Internalizing problems remained high and virtually unchanged* into the thirties
Young et al., 2019 (212)	Canada	Cohort study	<1000 g	Yes	1977–82	30–35	MINI, BAI, BDI, and sleep walking/talking, or trouble sleeping	*More symptoms of anxiety* and less likely to experience lifetime substance use disorder

Table 4 *(continued)*

Study**	**Country**	**Study design**	**BW (g), GA (wk)**	**Control group**	**Birth year**	**Age**	**Measurement**	**Outcome in EP-born vs term-born**
Räikkönen et al., 2008 (213)	Finland	Cohort study	<1500 g	Yes	1978–85	22	BDI, CES-D	*VLBW participants reported less depression*. However, VLBW-born AGA reported fewer depression symptoms, and SGA reported more depressive symptoms
Sammallahi et al., 2015 (214)	Finland	Cohort study	<1500 g	No	1978–85	25	ADHD, psychiatric problems, ASR	*No association* between growth and mental health
Hollund et al., 2023 (176)	Finland, Germany, UK, Ireland, Norway	Cohort study	<32 wk, <1500 g	Yes	1978–95	19–26	ASR	High levels of internalizing, externalizing, and overall problems on *mental health scales were associated* with heightened levels of pain and fatigue in both preterm- and term-born groups
Kroll et al., 2018 (215)	UK	Cohort study	<33 wk	Yes	1979–84	30	CAARMS	*More psychopathology problems*
Nataluci et al., 2013 (103)	Switzerland	Cohort study	<1000 g	Community norms	1983–5	23.3	BSI	*More mental health problems* in 4 of 9 dimensions: somatization, interpersonal sensitivity, hostility, and psychoticism
Hallin & Stjernqvist, 2011 (216)	Sweden	Cohort study	<29 wk	Yes	1985–6	18	YSR	*Fewer externalizing problems*

Table 4 *(continued)*

Study[**]	**Country**	**Study design**	**BW (g), GA (wk)**	**Control group**	**Birth year**	**Age**	**Measurement**	**Outcome in EP-born vs term-born**
Breeman et al., 2016 (178)	Germany	Cohort study	<32 wk, <1500 g	Yes	1985–6	6, 8, 26	CBCL, TRCB, TRAB, MEI	*More attention problems, more ADHD*
Lund et al., 2012 (208)[b]	Norway	Cohort study	<1500 g	Yes	1986–8	20	ASR	*More mental health problems*
Husby et al., 2016 (100)	Norway	Cohort study	<1500 g	Yes	1986–8	20, 23	ASR	*More internalizing problems*, and decline in mental health from 20 to 23 years
Lærum et al., 2019 (183)	Norway	Cohort study	<1500 g	Yes	1986–8	26	ASR	*More internalizing and externalizing problems*
Eriksen et al., 2023 (217)	Norway	Cohort study	<1500 g	Yes	1986–8	26	SDQ	*More mental health difficulties*. Emotional symptoms increased from 14 to 26 years in VLBW group. Hyperactivity and inattention did not decrease with age, in contrast to control group
Leijon et al., 2020 (218)	Sweden	Cohort study	<1500 g	Yes	1987–8	27–28	YSR, ASR	*No difference was found*
Burnett et al., 2014 (219)	Australia	Cohort study	<28 wk, <1000 g	Yes	1991–2	18	Clinical interview, questionnaires: BAI, CESD-R, BIS/BAS, PANAS, APSD, WASI	*More ADHD*

Table 4 *(continued)*

Study**	Country	Study design	BW (g), GA (wk)	Control group	Birth year	Age	Measurement	Outcome in EP-born vs term-born
Georgsdottir et al., 2013 (220)	Iceland	Cohort study	<1000 g	Yes	1991–5	13–18	YSR	*More internalizing and total problems*
Burnett et al., 2022 (131)	Australia	Cohort study	<28 wk, <1000 g	Yes	1991–2	18, 25	ADHD-RS, Structured Clinical Interview for DSM-IV Disorders, BAI, CESD-R	*No difference*

[*] Overview of studies on mental health comparing between EP/ELBW or VP/VLBW adults and term-born controls.

[**] The studies listed in the table were identified by using a search strategy on Medline, Embase, CINAHL, or APA PsycINFo, including the following search words: ‘infant, very low birth weight’, ‘infant, extremely low birth weight’ OR ‘infant, extremely premature’ OR ‘preterm’, ‘premature’, ‘very-low’, ‘very low’, ‘extremely-low’, ‘extremely low’, ‘birth-weight’ or ‘birth weight’ or ‘birthweight’ or ‘born or infant*’ or ‘child*’ or ‘adult’. AND ‘Adult’ or ‘adult*’ or ‘18 year*’ or ‘age* 18’ AND ‘mental health’ or ‘psychological well-being’, ‘asr’ or ‘YARS’ or ‘Young Adult Self-Report’ or ‘Adult Self-Report’ or ‘ASEBA’. Articles on diagnostic measurements were excluded, and articles on self-reported mental health were included. The references list of included papers were reviewed.

[a] Solely focused on studies concerning adults.

[b] Included in the meta-analysis by Pyhälä et al., 2017 (126).

[c] Included in the meta-analysis by Mathewson et al., 2017 (171).

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-RS, ADHD Rating Scale; AGA, appropriate for gestational age; APSD, Antisocial Process Screening Device; ASD, autism spectrum disorder; ASR, Adult Self-Report; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BIS/BAS, Behavioral Inhibition/Activation Systems Scales; BSI, Brief Symptom Inventory; BYI, Beck Youth Inventories of Emotional and Social Impairment; BW, birthweight; CAARMS, Comprehensive Assessment of At-Risk Mental State; CES-D, Center for Epidemiologic Studies Depression Scale; CESD-R, Center for Epidemiologic Studies Depression Scale—Revised; CSES, Coopersmith Self-Esteem Scale; DBD, disruptive behaviour disorder; ELBW, extremely low birthweight; EP, extremely preterm; GA, gestational age; MEI, Mannheimer Parent Interview; MINI, Mini International Neuropsychiatric Interview; OCHS-R, Ontario Child Health Study—Revised; PANAS, Positive and Negative Affect Schedule; RSES, Rosenberg Self-Esteem Scale; SGA, small for gestational age; SSS, Shyness and Sociability Scale; STAI, State-Trait Anxiety Inventory; TRAB, Tester's Rating of Adult Behavior; TRCB, Tester's Rating of Child Behavior; VLBW, very low birthweight; VP, very preterm; wk, week; y, year; YARS, Young Adult Self-Report.

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Appendix

APPENDIX I

Spørreskjema om barns helse - CHQ - CF 87

Til barn og ungdom

1. Vi vil gjerne spørre om hvordan du har det, hvordan du føler deg og aktiviteter du gjør hver dag. Svarene dine vil ikke bli vist til andre.
2. Deltagelsen er frivillig.
3. Du svarer ved sette kryss i en av rutene som ser slik ut: ☐ ☐
4. Selv om enkelte spørsmål kan se like ut, er det viktig at du svarer på alle spørsmålene.
5. Det finnes ingen riktige eller gale svar.

Del 1 Generell helse

1.1. Stort sett, vil du si at din helse er:

Utmerket	Meget god	God	Ganske god	Dårlig
☐	☐	☐	☐	☐

TAKK FOR AT DU SVARTE PÅ SPØRSMÅLENE!

Del 2 Fysisk aktivitet

2.1. I løpet av de siste 4 ukene , har det vært vanskelig for deg å gjøre noen av de følgende aktiviteter på grunn av helseproblemer?

	Ja, svært vanskelig	Ja, ganske vanskelig	Ja, litt vanskelig	Nei, ikke vanskelig
a. gjøre ting som krever **mye** anstrengelse som å spille fotball , løpe eller gå på tur?	☐	☐	☐	☐
b. gjøre ting som krever **ganske mye** anstrengelse, som å sykle eller gå på skøyter?	☐	☐	☐	☐
c. gå langt eller gå opp flere trapper?	☐	☐	☐	☐
d gå rundt i nabolaget, til lekeområde eller til skolen?	☐	☐	☐	☐
e. gå ett kort stykke eller gå opp en trapp?	☐	☐	☐	☐
f. hjelpe til hjemme?	☐	☐	☐	☐
g. sitte på huk, løfte noe eller bøye deg?	☐	☐	☐	☐
h. spise, kle på deg, bade eller gå på toalettet alene?	☐	☐	☐	☐
i. komme deg opp i og ut av sengen?	☐	☐	☐	☐

Del 3 Daglige aktiviteter

3.1. Har det, i løpet av de siste 4 ukene, vært vanskelig for deg å gjøre skolearbeid eller delta i vanlige aktiviteter med venner fordi du har følt deg TRIST eller ENGSTELIG?

Har det vært vanskelig å:	Ja, svært vanskelig	Ja, ganske vanskelig	Ja, litt vanskelig	Nei, ikke vanskelig
a. gjøre visse TYPER skolearbeid eller aktiviteter med venner	☐	☐	☐	☐
b. bruke like MYE tid som du pleier på skolearbeid eller aktiviteter med venner	☐	☐	☐	☐
c. GJØRE skolearbeid eller delta i aktiviteter med venner i det hele tatt	☐	☐	☐	☐

3.2. Har det, i løpet av de siste 4 ukene, vært vanskelig for deg å utføre skolearbeid eller vanlige aktiviteter med venner på grunn av problemer med din OPPFØRSEL?

Har det vært vanskelig å:	Ja, svært vanskelig	Ja, ganske vanskelig	Ja, litt vanskelig	Nei, ikke vanskelig
a. gjøre visse TYPER skolearbeid eller aktiviteter med venner	☐	☐	☐	☐
b. bruke like MYE tid som du pleier på skolearbeid eller aktiviteter med venner	☐	☐	☐	☐
c. GJØRE skolearbeid eller delta i aktiviteter med venner i det hele tatt	☐	☐	☐	☐

3.3. **Har det, i løpet av de siste 4 ukene, vært vanskelig for deg å utføre skolearbeid eller vanlige aktiviteter med venner på grunn av problemer med din FYSISKE helse?**

Har det vært vanskelig å:	Ja, svært vanskelig	Ja, ganske vanskelig	Ja, litt vanskelig	Nei, ikke vanskelig
a. gjøre visse TYPER skolearbeid eller aktiviteter med venner?	☐	☐	☐	☐
b. bruke like MYE tid som du pleier på skolearbeid eller aktiviteter med venner?	☐	☐	☐	☐
c. GJØRE skolearbeid eller delta i aktiviteter med venner i det hele tatt?	☐	☐	☐	☐

Del 4 Om å ha vondt

4.1. **I løpet av de siste 4 ukene, hvor mye vondt eller hvor sterke smerter har du hatt?**

☐	☐	☐	☐	☐	☐
Ingen	Meget svake	Svake	Moderate	Sterke	Svær sterke

4.2. **I løpet av de siste 4 ukene, hvor ofte har du hatt smerter eller vondt?**

☐	☐	☐	☐	☐	☐
Aldri	En eller to ganger	Noen få ganger	Ganske ofte	Meget ofte	Hver dag eller nesten hver dag

Del 5 Om deg selv

5.1. I løpet av de siste 4 ukene, hvor ofte kunne hver av de følgende uttalelser beskrive deg?

	Svært ofte	Ganske ofte	Noen ganger	Nesten aldri	Aldri
a. oppført deg barnslig?	☐	☐	☐	☐	☐
b. kranglet?	☐	☐	☐	☐	☐
c. hatt vanskelig for å konsentrere deg?	☐	☐	☐	☐	☐
d. latt være å gjøre som læreren eller foreldrene dine har bedt deg om?	☐	☐	☐	☐	☐
e. villet være alene?	☐	☐	☐	☐	☐
f. løyet eller jukset?	☐	☐	☐	☐	☐
g. hatt problemer med å bli likt?	☐	☐	☐	☐	☐
h. følt deg kløneete?	☐	☐	☐	☐	☐
i. rømt hjemmefra?	☐	☐	☐	☐	☐
j. hatt talevansker (for eksempel stamming)?	☐	☐	☐	☐	☐
k. stjålet noe hjemme?	☐	☐	☐	☐	☐
l. stjålet noe borte?	☐	☐	☐	☐	☐

	Svært ofte	Ganske ofte	Noen ganger	Nesten aldri	Aldri
m blitt sur hvis du ikke har fått det som du ville?	☐	☐	☐	☐	☐
n. blitt skikkelig sint hvis du ikke har fått det som du ville?	☐	☐	☐	☐	☐
o. syntes det har vært vanskelig å være sammen med andre?	☐	☐	☐	☐	☐
p. syntes det har vært vanskelig å være venner?	☐	☐	☐	☐	☐

5.2. Sammenliknet med andre barn på din alder, vil du si at din oppførsel er:

Utmerket	Meget god	God	Ganske god	Dårlig
☐	☐	☐	☐	☐

Del 6 Følelser og humør

6.1. I løpet av de siste fire ukene, hvor stor del av tiden har du:

	Hele tiden	Nesten hele tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
a. følt deg trist?	☐	☐	☐	☐	☐
b. hatt lyst til å gråte?	☐	☐	☐	☐	☐

	Hele tiden	Nesten hele tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
c. følt deg redd eller skremt?	☐	☐	☐	☐	☐
d. bekymret deg for ting?	☐	☐	☐	☐	☐
e. følt deg ensom?	☐	☐	☐	☐	☐
f. vært ulykkelig?	☐	☐	☐	☐	☐
g. vært nervøs?	☐	☐	☐	☐	☐
h. følt deg irritert eller sint?	☐	☐	☐	☐	☐
i. vært glad?	☐	☐	☐	☐	☐
j. vært i godt humør?	☐	☐	☐	☐	☐
k. trivdes med det du gjør?	☐	☐	☐	☐	☐
l. hatt det morsomt?	☐	☐	☐	☐	☐
m. følt deg rastløs?	☐	☐	☐	☐	☐
n. hatt problemer med å sove?	☐	☐	☐	☐	☐
o. hatt hodepine?	☐	☐	☐	☐	☐
p. likt deg selv?	☐	☐	☐	☐	☐

Del 7 Selvtillit

7.1. **I løpet av de <u>siste 4 ukene</u>, hvor fornøyd har du vært med:**

	Svært fornøyd	**Ganske fornøyd**	**Hverken fornøyd eller misfornøyd**	**Nokså mis-fornøyd**	**Svært mis-fornøyd**
a. deg selv?	☐	☐	☐	☐	☐
b. skolearbeidet ditt?	☐	☐	☐	☐	☐
c. hvor flink du er i idrett?	☐	☐	☐	☐	☐
d. vennene dine?	☐	☐	☐	☐	☐
e. de tingene du KAN?	☐	☐	☐	☐	☐
f. hvordan du kommer overens med andre?	☐	☐	☐	☐	☐
g. kroppen og utseendet ditt?	☐	☐	☐	☐	☐
h. hvordan du stort sett føler deg?	☐	☐	☐	☐	☐
i. hvordan du kommer overens med familien?	☐	☐	☐	☐	☐
j. livet ditt?	☐	☐	☐	☐	☐
k. deg selv som venn?	☐	☐	☐	☐	☐
l. hva andre synes om deg?	☐	☐	☐	☐	☐
m. hvor flink du er til å snakke med andre?	☐	☐	☐	☐	☐
n. helsen din?	☐	☐	☐	☐	☐

Seksjon 8 Helse

8.1. **Hvor riktig eller gal er hver av de følgende påstander for deg?**

	Helt riktig	**Delvis riktig**	**Vet ikke**	**Delvis gal**	**Helt gal**
a. Min helse er utmerket.	☐	☐	☐	☐	☐
b. En gang var jeg så syk at jeg trodde jeg skulle dø.	☐	☐	☐	☐	☐
c. Jeg pleier ikke å bli så veldig syk.	☐	☐	☐	☐	☐
d. Jeg tror ikke jeg er like frisk som andre barn jeg kjenner.	☐	☐	☐	☐	☐
e. Jeg har aldri vært <u>veldig</u> syk	☐	☐	☐	☐	☐
f. Jeg blir <u>alltid</u> syk.	☐	☐	☐	☐	☐
g. Jeg tror jeg kommer til å få dårligere helse når jeg blir eldre.	☐	☐	☐	☐	☐
h. Jeg tror jeg kommer til å ha veldig god helse når jeg blir eldre.	☐	☐	☐	☐	☐
i. Jeg bekymrer meg aldri om helsen min.	☐	☐	☐	☐	☐
j. Jeg føler meg frisk nå.	☐	☐	☐	☐	☐
k. Jeg tror jeg bekymrer meg mer for min helse enn andre på min alder.	☐	☐	☐	☐	☐

8.2. Sammenliknet med for ett år siden, hvordan vil du vurdere helsen din nå:

☐	☐	☐	☐	☐
Mye bedre nå enn for 1 år siden	Litt bedre nå enn for 1 år siden	Omtrent den samme nå som for 1 år siden	Litt dårligere nå enn for 1 år siden	Mye dårligere nå enn for 1 år siden

Del 9 Familien

9.1. I løpet av de siste 4 ukene, hvor ofte har din helse eller atferd:

	Svært ofte	Ganske ofte	Noen ganger	Nesten aldri	Aldri
a. begrenset de aktivitetene familien kunne gjøre sammen?	☐	☐	☐	☐	☐
b. avbrutt forskjellige daglige familie aktiviteter (måltider, se på TV)?	☐	☐	☐	☐	☐
c. begrenset familiens muligheter til å gjøre noe på kort varsel?	☐	☐	☐	☐	☐
d. ført til spenning eller konflikter i hjemmet?	☐	☐	☐	☐	☐
e. vært en årsak til uenighet eller krangling i familien?	☐	☐	☐	☐	☐
f. gjort at familien har måttet forandre eller avlyse planer i siste liten?	☐	☐	☐	☐	☐

9.2. Iblant har familier problemer med å fungere sammen. De er ikke alltid enige og de kan bli sinte på hverandre. Stort sett, hvordan vil du vurdere din families evne til å fungere sammen?

Utmerket	Meget god	God	Nokså god	Dårlig
☐	☐	☐	☐	☐

Del 10 Om deg selv

10.1. Er du : Gutt ☐ **eller** Jente ☐

10.4. Har du noen gang søkt hjelp hos noen på skolen, helsestasjon eller legekontor for :

	Ja	Nei
	(Kryss for Ja eller Nei ved hvert spørsmål)	
a. Skader som følge av ulykker?	☐	☐
b. Sengevæting?	☐	☐
c. Brystsmerter?	☐	☐
d. Diare eller forstoppelse?	☐	☐
e. Langvarig slapphet?	☐	☐
f. Hodepine?	☐	☐
g. Dårlig matlyst over tid?	☐	☐
h. Mareritt eller søvnproblemer?	☐	☐
i. Magesmerter?	☐	☐

TAKK FOR AT DU SVARTE PÅ SPØRSMÅLENE!

APPENDIX II

RAND-36 Din helse

Spørsmålene under handler om hvordan du oppfatter helsen din. Disse opplysningene vil hjelpe oss til å forstå hvordan du føler deg og hvor godt du er i stand til å utføre dine vanlige aktiviteter.

Hvert spørsmål skal besvares ved å sette et kryss (X) i den boksen som passer best for deg.

1. Stort sett, vil du si at helsen din er:

Utmerket	Veldig god	God	Nokså god	Dårlig
☐	☐	☐	☐	☐

2. Sammenlignet med for ett år siden, hvordan vil du si at helsen din stort sett er nå?

Mye bedre nå enn for ett år siden	Litt bedre nå enn for ett år siden	Omtrent som for ett år siden	Litt dårligere nå enn for ett år siden	Mye dårligere nå enn for ett år siden
☐	☐	☐	☐	☐

3. De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er helsen din slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, hvor mye? [Kryss (X) en boks på hver linje.]

		Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
a	**Anstrengende aktiviteter** som å løpe, løfte tunge gjenstander, delta i anstrengende idrett	☐	☐	☐
b	**Moderate aktiviteter** som å flytte et bord, støvsuge, gå en spasertur eller drive med hagearbeid	☐	☐	☐
c	Løfte eller bære poser med dagligvarer	☐	☐	☐
d	Gå opp trappen **flere** etasjer	☐	☐	☐
e	Gå opp trappen **én** etasje	☐	☐	☐
f	Bøye deg eller gå ned på kne	☐	☐	☐
g	Gå **mer enn to kilometer**	☐	☐	☐
h	Gå **flere hundre meter**	☐	☐	☐
i	Gå **hundre meter**	☐	☐	☐
j	Dusje eller kle på deg	☐	☐	☐

RAND Corporation, USA, har opphavsrett til det opprinnelige skjemaet, som ble utviklet innen Medical Outcomes Study.
Nasjonalt kunnskapssenter for helsetjenesten distribuerer oversettelsen av RAND-36, norsk versjon 1.

4. I løpet av de siste fire ukene, har du hatt noen av de følgende problemene i arbeidet ditt eller i andre daglige aktiviteter på grunn av din fysiske helse?

		Ja	Nei
a	Kuttet ned på **hvor mye tid** du brukte på arbeid eller andre aktiviteter	☐	☐
b	**Fått gjort mindre** enn du ønsket	☐	☐
c	Vært begrenset i type **arbeidsoppgaver** eller andre aktiviteter	☐	☐
d	Hatt **problemer** med å utføre arbeidet eller andre aktiviteter (for eksempel at det krevde en ekstra innsats av deg)	☐	☐

5. I løpet av de siste fire ukene, har du hatt noen av de følgende problemene i arbeidet ditt eller i andre daglige aktiviteter på grunn av følelsesmessige problemer (som å føle seg engstelig eller deprimert)?

		Ja	Nei
a	Kuttet ned på **hvor mye tid** du brukte på arbeid eller andre aktiviteter	☐	☐
b	**Fått gjort mindre** enn du ønsket	☐	☐
c	Utført arbeid eller andre aktiviteter **mindre grundig** enn vanlig	☐	☐

6. I løpet av de siste fire ukene, i hvilken grad har den fysiske helsen din eller følelsesmessige problemer påvirket dine vanlige sosiale aktiviteter med familie, venner, naboer eller andre grupper mennesker?

Ikke i det hele tatt	Litt	Moderat	Ganske mye	Ekstremt mye
☐	☐	☐	☐	☐

7. Hvor mye kroppslige smerter har du hatt i løpet av de siste fire ukene?

Ingen	Veldig svake	Svake	Moderate	Sterke	Veldig sterke
☐	☐	☐	☐	☐	☐

RAND Corporation, USA, har opphavsrett til det opprinnelige skjemaet, som ble utviklet innen Medical Outcomes Study.
Nasjonalt kunnskapssenter for helsetjenesten distribuerer oversettelsen av RAND-36, norsk versjon 1.

8. I løpet av de siste fire ukene, hvor mye har smerter påvirket det vanlige arbeidet ditt (gjelder både arbeid utenfor hjemmet og husarbeid)?

Ikke i det hele tatt	Litt	Moderat	Ganske mye	Ekstremt mye
☐	☐	☐	☐	☐

9. De neste spørsmålene handler om hvordan du føler deg og hvordan du har hatt det i løpet av de siste fire ukene. For hvert spørsmål, ber vi deg velge det svaret som best beskriver hvordan du har følt deg.

Hvor ofte i løpet av de siste fire ukene:

		Hele tiden	Mesteparten av tiden	En god del av tiden	Noe av tiden	Litt av tiden	Aldri
a	Har du følt deg full av liv?	☐	☐	☐	☐	☐	☐
b	Har du vært veldig nervøs?	☐	☐	☐	☐	☐	☐
c	Har du følt deg så langt nede at ingenting kunne gjøre deg glad?	☐	☐	☐	☐	☐	☐
d	Har du følt deg rolig og avslappet?	☐	☐	☐	☐	☐	☐
e	Har du hatt mye overskudd?	☐	☐	☐	☐	☐	☐
f	Har du følt deg nedfor og deprimert?	☐	☐	☐	☐	☐	☐
g	Har du følt deg utslitt	☐	☐	☐	☐	☐	☐
h	Har du følt deg glad?	☐	☐	☐	☐	☐	☐
i	Har du følt deg sliten?	☐	☐	☐	☐	☐	☐

10. I løpet av de siste fire ukene, hvor mye av tiden har den fysiske helsen din eller følelsesmessige problemer påvirket dine sosiale aktiviteter (som å besøke venner, slektninger osv.)?

Hele tiden	Mesteparten av tiden	En del av tiden	Litt av tiden	Aldri
☐	☐	☐	☐	☐

RAND Corporation, USA, har opphavsrett til det opprinnelige skjemaet, som ble utviklet innen Medical Outcomes Study.
Nasjonalt kunnskapssenter for helsetjenesten distribuerer oversettelsen av RAND-36, norsk versjon 1.

11. Hvor RIKTIG eller GAL er hver av de følgende påstandene for deg?

		Helt riktig	Stort sett riktig	Vet ikke	Stort sett galt	Helt galt
a	Det virker som om jeg blir syk litt lettere enn andre	☐	☐	☐	☐	☐
b	Jeg er like frisk som de fleste jeg kjenner	☐	☐	☐	☐	☐
c	Jeg regner med at helsen min blir dårligere	☐	☐	☐	☐	☐
d	Helsen min er utmerket	☐	☐	☐	☐	☐

RAND Corporation, USA, har opphavsrett til det opprinnelige skjemaet, som ble utviklet innen Medical Outcomes Study.
Nasjonalt kunnskapssenter for helsetjenesten distribuerer oversettelsen av RAND-36, norsk versjon 1.

APPENDIX III Table III Linguistic differences between SF-36 and RAND-36 translated into Norwegian.

Spørsmål	SF-36	RAND-36
1. Stor sett, vil du si at helsen din er:	Meget god, ganske god	Veldig god, nokså god
3.c	En handlekurv	Poser med dagligvarer
3.f	Sitte på huk	Gå ned på kne
3.h	Gå noen hundre meter	Gå flere hundre meter
3.j	Vaske deg	Dusje
4.a	Har du redusert tiden du har brukt på arbeidet ditt eller andre aktiviteter	Kuttet ned på hvor mye tid du brukte på arbeid eller andre aktiviteter
4.b	Har du utrettet mindre enn du hadde ønsket	Fått gjort mindre enn du ønsker
4.c	Har du vært hindret i visse typer arbeid eller andre aktiviteter	Vært begrenset i type arbeidsoppgaver eller andre aktiviteter
4.d	Har du hatt vanskeligheter med å utføre arbeidet ditt eller andre aktiviteter (f.eks. fordi det krevde ekstra anstrengelser)	Hatt problemer med å utføre arbeid eller andre aktiviteter (for eksempel at det krevde en ekstra innsats av deg)
5.a	Redusert	Kuttet
5.b	Utrettet	Gjort
9.a	Tiltakslyst	Liv
9.d	Harmonisk	Avslappet

APPENDIX IV

Health behaviour in school-aged children-symptom check list (HBSC-SCL)

42. **Hvor ofte har du brukt reseptfrie medisiner mot følgende plager i løpet av <u>de siste 3 månedene</u>?** *(sett ett kryss pr. linje)*

	Sjelden /aldri	1-3g /uke	4-6g /uke	Dag-lig
•Hodepine	☐	☐	☐	☐
•Muskel-/leddsmerter	☐	☐	☐	☐
•Magesmerter	☐	☐	☐	☐
•Ryggsmerter	☐	☐	☐	☐
•Andre plager	☐	☐	☐	☐

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	**Saksbehandler:**	**Telefon:**	**Vår dato:**	**Vår referanse:**
REK vest	Trine Anikken Larsen	55978498	16.05.2017	2017/628/REK vest
			Deres dato:	**Deres referanse:**
			28.03.2017	

Vår referanse må oppgis ved alle henvendelser

Thomas Halvorsen
BARNE og UNGDOMSKLINIKKEN

2017/628 Født for tidlig - konsekvenser for lungehelse og funksjon

Forskningsansvarlig: Helse Bergen HF - Haukeland universitetssykehus
Prosjektleder: Thomas Halvorsen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK vest) i møtet 27.04.2017. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektomtale

Prosjektet er en videreføring av en studie som har pågått siden 2001. Formålet er å studere hvordan ekstremt tidlig fødsel påvirker senere fysisk og psykisk helse, livskvalitet og daglig funksjon. Forskergruppen ønsker å bruke helseopplysninger fra pasientjournaler som tidligere ble godkjent i prosjekt med REK-nummer 240.07. Helseopplysningene skal brukes til å studere forhold i fosterlivet, barndom eller senere som har betydning for fysisk og psykisk helse, livskvalitet og daglig funksjon i voksen alder. Deltakerne kommer fra tre populasjonsbaserte fødselskohorter ved nyfødtavdelingene i Bergen og Stavanger.

Vurdering

Forsvarlighet

Prosjektet er en oppfølging fra en studie som har pågått siden 2001. Deltakerne skal gjennomføre de samme testene som tidligere, samt svare på spørreundersøkelse. Komiteen vurderer studien til å være forsvarlig.

Datainnsamling

Forskergruppen skal innhente opplysninger om tidligere diagnoser, sykdommer, tilstander, skader eller behandlinger som kan forklare eventuelle avvik som påvises i denne studien. Dette vil gjelde forhold i graviditet, fødsel, nyfødtperiode og livet frem til inklusjon i studien. I tillegg skal det gjennomføres vanlig klinisk undersøkelse, undersøkelse av lungefunksjon, samt undersøkelse av hjerte og sirkulasjon. Deltakerne skal løpe på tredemølle for måling av maksimalt surstoffopptak, i tillegg til å svare på spørreundersøkelse. Komiteen har ingen innvendinger til dette.

Registerdata

Det oppgis i søknaden at forskergruppen i utgangspunktet ikke ønsker tilgang til registerdata per i dag, men at de likevel ønsker å holde muligheten åpen for dette på et senere tidspunkt. Deltakerne informeres om at det kan bli aktuelt å koble registerdata gjennom informasjonsskrivet. Komiteen godkjenner at registerdata kan kobles, men forutsetter at det sendes inn en endringsmelding om dette dersom det blir aktuelt. Det må spesifiseres hvilke registre data skal kobles med.

Besøksadresse:
Armauer Hansens Hus (AHH), Tverrfløy Nord, 2 etasje. Rom 281. Haukelandsveien 28

Telefon: 55975000
E-post: rek-vest@uib.no
Web: http://helseforskning.etikkom.no/

All post og e-post som inngår i saksbehandlingen, bes adressert til REK vest og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee, REK vest, not to individual staff

Overføring av helseopplysninger til utlandet
Helseopplysninger skal overføres til Nederland og Australia. REK vest har ingen innvendinger til dette så fremt bruken av opplysninger utelukkende anvendes til studiens formål, og ingen prøver eller identifiserbar informasjon lagres utover prosjektperioden.

Ny spesifikk forskningsbiobank
Det skal opprettes en ny spesifikk forskningsbiobank med tittel "Født for tidlig - konsekvenser for lungehelse og funksjon", hvor Thomas Halvorsen er ansvarshavende. Komiteen forstår det slik at forskningsbiobanken opphører når prosjektet er avsluttet. Komiteen har ingen merknader til dette.

Genetiske undersøkelser
Det oppgis i søknaden at det skal gjøres genetiske undersøkelser av det biologiske materialet. Prosjektleder oppgir at undersøkelsene ikke vil ha behandlingsmessige eller diagnostiske konsekvenser for den enkelte og at resultater ikke skal tilbakeføres til den enkelte. Genetiske undersøkelser vil således kun være aktuelt for pasientgruppen, ikke kontrollgruppen. Komiteen har ingen innvendinger til dette, men påpeker at forskergruppen må søke REK om godkjenning gjennom endringsmelding dersom genetiske undersøkelser vil bli aktuelt i studien.

Rekruttering
Komiteen oppfatter det slik at forskergruppen skal sende ut den første informasjonen om studien per brev til deltakerne. Dersom noen ikke svarer på den første henvendelsen, ønsker forskergruppen tillatelse til å kontakte de aktuelle deltakerne på en annen måte, det vil si enten på telefon, SMS eller e-post.

Komiteen godkjenner at informasjon om studien sendes per brev. En eventuell påminnelse om deltakelse til de som ikke har svart innen en viss frist, kan gis enten på SMS eller e-post. Telefonisk kontakt utenom SMS godkjennes ikke.

Informasjonsskriv
Komiteen påpeker at det må spesifiseres hvilke data som forskergruppen ønsker å koble i informasjonsskrivet. I tillegg må dato for prosjektslutt angis. Komiteen ber om at revidert informasjonsskriv sendes til REK vest til e-postadressen post@helseforskning.etikkom.no før prosjektet igangsettes.

Prosjektslutt og håndtering av data
Dato for prosjektslutt er satt til 30.04.2032. Det oppgis i søknaden at forskergruppen ønsker å oppbevare avidentifiserte forskningsdata etter prosjektslutt.

Det fremgår av helseforskningsloven § 38 at opplysninger ikke skal oppbevares lenger enn det som er nødvendig for å gjennomføre prosjektet. REK kan bestemme at forskningsdata kan oppbevares i inntil fem år for etterkontroll. Komiteen godkjenner at data i dette prosjektet kan oppbevares i inntil fem år etter prosjektslutt. Dersom det er behov for forlengelse av prosjektperioden, må det sendes inn endringsmelding til REK.

Vilkår

- Informasjonsskrivet må endres i henhold til komiteens merknader.

Vedtak

REK vest godkjenner prosjektet på betingelse av at ovennevnte vilkår tas til følge.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK vest på eget skjema senest 31.10.2032, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK vest dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Marit Grønning
Prof. dr.med
Komiteleder

Trine Anikken Larsen
seniorkonsulent

Kopi til:postmottak@helse-bergen.no

APPENDIX VI Table VI Characteristics at 34 years follow up, of the participated and non-participated subjects born extremely preterm (EP).

	Participated (n = 35)	**Not participated (n = 14)**	**Participated VS not participated.**	
			Difference between mean (95%CI)	**P-value**
Female, *n (%)*	16 (72.7)	6 (27.3)		0.856
Male, n (%)	19 (70.4)	8 (29.6)		
Gestational age, weeks, mean (SD)	27.50 (1.5)	27.14 (1.4)	0.543 (-0.456, 1.541)	0.276
Birth weight, mean (SD)	1002.03 (193.5)	1010.0 (190.9)	-7.971 (-132.97, 117.03)	0.897
Severe disability	6	2		
Without severe disability	29	11		
Neurosensory impairments, n				
Disabling CP[a]	2	0		
Non-disabling CP[a]	2	0		
Deaf	2	1		
Blind	0	3		

Comparison of categorical data were made using Pearsons χ^2 test or Fisher's exact mid-p test, independent samples t-test for normally distributed continuous data.

APPENDIX VII Table VII Self-reported HRQoL at 34-years of age in EP-born with and without bronchopulmonary dysplasia (BPD).

SF-36 domains	EP with BPD (n = 10) Mean rank	EP without BPD (n = 24) Mean rank	p-value*
Physical Functioning	19.75	16.56	0.401
Role Physical	21.50	16.60	0.212
Bodily Pain	17.10	17.67	0.897
General Health	17.90	17.33	0.897
Vitality	18.40	17.84	0.900
Social Functioning	19.30	17.48	0.653
Role Emotional	19.35	17.46	0.627
Mental Health	18.25	17.90	0.928

*Independent-Samples Mann-Whitney U Test, p-value < 0.005 indicates statistical significance.

Paper I, II and III

Benestad *et al.*
Health and Quality of Life Outcomes (2022) 20:112
https://doi.org/10.1186/s12955-022-02018-5

Health and Quality of Life Outcomes

RESEARCH

Open Access

Development of health-related quality of life and subjective health complaints in adults born extremely preterm: a longitudinal cohort study

Merete Røineland Benestad[1,2*], Jorunn Drageset[2,3], Geir Egil Eide[2,5], Maria Vollsæter[1,4], Thomas Halvorsen[4] and Bente Johanne Vederhus[1,3]

Abstract

Purpose: To study development trajectories to 34 years of age of health-related quality of life (HRQoL) and subjective health complaints in extremely preterm (EP) born subjects with and without disability, and to compare with term-born controls.

Methods: A Norwegian longitudinal population-based cohort of subjects born in 1982–85 at gestational age ≤ 28 weeks or with birth weight ≤ 1000 g and matched term-born controls completed the Norwegian version of the Short Form Health Survey-36 at ages 24 and 34 and the Health Behaviour in School-aged Children–Symptom Checklist at ages 17, 24 and 34 years. Data were analysed by unadjusted and adjusted mixed effects analyses with time by subject group as interaction term.

Results: A total of 35/49 (73%) surviving EP-born and 36/46 (78%) term-born controls participated at this third follow-up. EP-born subjects with severe disability reported clinical significant lower mean score in all domains compared to the term-born controls. Healthy EP-born subjects reported significantly lower mean scores for vitality, role emotional and mental health, and significantly higher mean score for total and psychological health complaints compared to term-born controls. There were no significant interactions with age regarding HRQoL and somatic health complaints, while there were significant differences in psychological health complaints; the EP-born scored higher at age 24 and lower at age 34.

Conclusions: EP-born adults at age 34 reported inferior HRQoL versus term-born peers, especially in the mental health domains, indicating that the negative differences observed at 24 years remained unchanged.

Keywords: Quality of life, SF-36, Infant, extremely premature, Self-rated health, Subjective health complaints, Preterm adults, Longitudinal cohort

Introduction

Since the 1980s survival after extremely preterm (EP) birth has gradually become the rule rather than the exception in high-income countries. Currently, more than 90% survive birth at 27 weeks gestation, which is considered cut-off for being labelled EP, and these infants now constitute 1 in 200 children growing up [1]. Birth at this early stage of pregnancy implies that growth and development normally taking place in a protected intrauterine environment, instead must take place in a neonatal intensive care unit (NICU). Survival often requires comprehensive and invasive intensive care measures which also may be harmful to

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immature and highly vulnerable infants. Additionally, preterm birth happens for a reason, and the infant carries the burden of whatever pathology that led to the early delivery. Childhood and adolescent consequences of this scenario are fairly well-known, whereas the lifelong implications are virtually undescribed, simply because their high survival rates are so recent achievements [2–4].

Several studies have reported cognitive and social limitations, neurosensory deficiencies, mental health problems, psychiatric disorders, and pulmonary, cardiovascular and metabolic abnormalities in EP-born children and adolescents [5–9]. Low gestational age (GA) and low birthweight (BW) have been linked to low educational levels, special educational needs, low income and unemployment [10–16]. These issues all affect health-related quality of life (HRQoL), a concept that refers to the relationships between an individual's health and ability to function and their perceived wellbeing [17]. HRQoL is multidimensional and includes domains related to physical, mental, emotional and social functioning as well as the social context in which people live, and is acknowledged by major governmental bodies as a fundamental measure of health [18]. The knowledge on HRQoL in EP-born young adults is slowly increasing, but the data is equivocal and development beyond 30 years of age still uncharted territory [14, 19, 20]. In 2008, a systematic review concluded that the effects of preterm birth on HRQoL seem to diminish over time [19]. Later publications have challenged this notion, reporting inferior HRQoL in preterm born young adults, and a recent review from 2020 concluded it was not possible to conclude on this issue [20–22]. When it comes to EP-born with disabilities, it is reported inferior HRQoL vs. EP-born without disabilities and vs. term-born (TB) controls [23].

We have previously reported on HRQoL and subjective health complaints at 17 and 24 years of age in a population based Norwegian cohort born EP. At age 17, the EP-born did not differ from their term-born peers; however, when faced with the challenges of adult life at age 24, their mental and social HRQoL had deteriorated and psychological health complaints had increased [24]. The present study is an extension of this study, performed at 34 years of age. We aimed to (1) describe self-perceived HRQoL and subjective health complaints at 34 years of age in EP-born subjects with and without disability and term-born controls, and (2) investigate and compare longitudinal development of HRQoL from 24 to 34 years of age, and subjective health complaints at 17, 24 and 34 years.

Methods

Study design and participants

This was a longitudinal population-based study. All subjects born *by mothers living within a defined area in western Norway (the counties Hordaland and Sogn og Fjordane) during the period* January 1982 and December 1985 at GA equal to or below 28 weeks or with BW equal to or below 1000 g where invited and included. *Eligible individuals were identified* based on the birth and admission protocols at the NICU of Haukeland University Hospital, the only unit in the region treating EP-born children. The temporally nearest term-born child of the same gender with BW between three and four kilograms (Norwegian 10–90 centiles) were invited as control. If that subject declined, the next born subject was approached, and so on until one term-born child was recruited for each enrolled EP-born.

The first follow-up took place in 2001–2002 at 17 years, the second was conducted during 2008–2009 at 24 years, and the third during 2018–2020 at 34 years of age. All assessments were performed at Haukeland University Hospital, where participants went through advanced studies of lung and exercise capacity [25, 26] and completed the questionnaires. Some few participants ($n = 3$) completed the questionnaires at home and returned by post.

Measures

The questionnaires applied at the third follow-up at age 34 years covered the same topics as the previous two follow-ups at 17 and 24 years.

Socio-demographic and clinical data

The information on socio-demographic data was obtained from a custom-made questions used in Norwegian population studies (http://www.hunt.ntnu.no). Educational level had originally a five-point response option with college/university more than 4 years as the most advanced. Employment had originally four response options (working, student, unemployed, or disability pension), whereas living arrangement had two response options (single or married/cohabitant). For the purpose of the statistical analyses in these relatively small populations, the categories were dichotomized. The medical history was obtained from the participants themselves and from hospital records.

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

HRQoL was measured using the Short-Form Health Survey (SF-36) version 1.1 at age 24 and the RAND-36 survey at age 34 [27]. The RAND-36 questionnaire was developed by the RAND Corporation [27]. It is considered equivalent to the SF-36, except minor differences regarding the scoring procedure of the two sub-scales "general health" and "bodily pain"; still, with extremely high correlation between SF-36 and RAND-36 ($r = 0.99$) [28]. For the purpose of this article, RAND-36 is hereafter referred to as SF-36. The questionnaire 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), mental health (five items) and one item assesses the perceived change in health status. Except for the two role-functioning scales with dichotomized response choices, the responses are rated along a three to six-point Likert-type scale. The preceding four weeks constitute 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 [17, 27]. Generally; a change of 5–10 points on a 0–100 scale is considered clinically significant [29]. The questionnaire is a broadly evaluated health status instrument with good reliability and validity [27]. The translated and validated Norwegian version was applied, which was tested for internal consistency by Cronbach's alpha and floor and ceiling effect [30, 31].

Health behaviour in school-aged children-symptom check list (HBSC-SCL)

Participants' subjective health complaints were measured using the Health Behaviour in School-aged Children—Symptom Check List (HBSC-SCL), which assesses the occurrence of four somatic (headache, abdominal pain, backache, and feeling dizzy) and four psychological symptoms (feeling low/depressed, irritable/ bad tempered, nervous and sleeping difficulties) [32]. The participants were asked to rate the frequency of symptoms experienced in the past 6 months. Each item was assessed on a 5-point response scale ranging from daily (4) to rarely/never (0). Two sub-scores (0–16) and a total sum-score (0–32) were calculated, higher scores indicate more symptoms [32]. We applied the translated and validated Norwegian version [33], that has revealed satisfactory reliability in test–retest analyses, ranging from 0.70 to 0.80.

Statistical analysis

The statistical package SPSS version 26.0 (SPSS Inc. Chicago, IL, US) was used. Demographic characteristics of the participants were analyzed using appropriate summary statistics for continuous and categorical variables. Further we used Welch's *t*-test and Fisher's Exact test to examine characteristics differences between EP-born and term-born controls. Results are reported with counts, proportions, means and standard deviations (SDs). The studies of HRQoL were parts of a comprehensive longitudinal assessment where statistical power had been calculated based on lung function data.

Sub-group analyses were preformed of the EP-born participants according to presence or absence of severe disability (healthy versus severe disability) defined by disabling cerebral palsy (CP), deafness or severe hearing loss, blindness or severe vision impairment.

We also preformed sub-group analyses of the EP-born participants by presence or absence of a neonatal history of bronchopulmonary dysplasia (BPD) which was defined by requirement for oxygen therapy at 36 weeks gestational age.

Mixed linear models were used to compare the EP and term-born groups. The matched structure of the EP and term-born participants (gender and age) and the repeated responses (17, 24 and 34 years for the HBSC-SCL and 24 and 34 years for the SF-36) were accounted for by assuming a covariance structure of unstructured correlation type. This method allows for contribution also from pairs with declines or who could not participate for some reason. The mean scores of the different domains were entered separately as dependent variables, whereas age and group were entered as independent variables with an interaction term to assess if group differences varied by age. Analyses were performed unadjusted and adjusted for gender, education and employment status. The criterion for statistical significance was p-value ≤ 0.05.

Ethics

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

Results

Eighty-one EP-born were admitted to the NICU during the inclusion period, 51 (63%) were alive at the first follow-up in 2001–02, of whom 46 (90%) participated. At second (2008–09) and third (2018–20) follow-up,

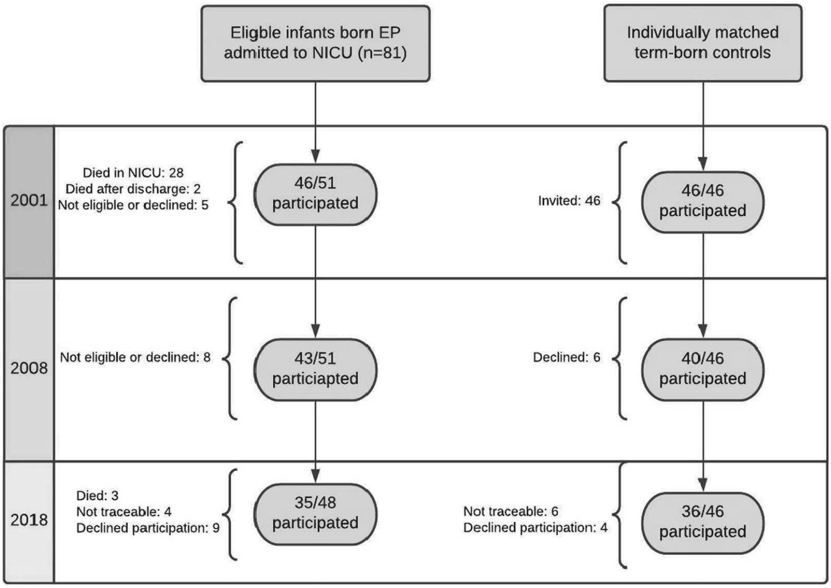

Fig. 1 Flow chart of the 81 extremely preterm (EP) born subjects and 46 matched term-born controls at the three follow-up time points. *NICU* neonatal intensive care unit

respectively 43/51 (84%) and 35/48 (73%) participated (Fig. 1). Corresponding numbers for the term-born controls were 46/46 (100%), 40/46 (87%) and 36/46 (78%), respectively.

The first and second follow-up

Results from the first and second follow-up has been described in detail elsewhere [24].

Demographic and clinical characteristics at 34 years of age (third follow-up)

Table 1 describes the participants' birth characteristics, education, employment and civil status. The age range was 32–36 years. EP-born participants had lower educational level compared to term-born controls, seven EP-born had no daily work compared to one term-born.

HRQoL at 34 years of age (third follow-up)

Results are reported in Table 2. Due to missing data in pairs, the descriptive sub-group analyses were based on 5 pairs of EP-born with severe disability and 19 pairs of healthy EP-born with their respective term-born controls. The EP-born with severe disability scored clinical significant poorer than term-born in all domains, this was statistical significant for mental health. For the healthy EP-born participants, there were statistical significant differences vs. the term-born in several domains; vitality, role emotional and mental health. No statistical differences was found between EP-born with and without BPD (data not shown).

Subjective health complaints at 34 years of age (third follow-up)

Results are reported in Table 2. Due to missing data in pairs, the descriptive sub-group analyses were based on 4 pairs of EP-born with severe disability and 19 pairs of healthy EP-born with their respective term-born controls. There were no statistical significant differences between the EP-born subjects with severe disability and term-born controls in self-rated somatic and psychological health complaints. For healthy EP-born vs. term-born subjects, there were a significant difference in total subjective health complaints and the sub-score psychological complaints.

Developmental of HRQoL from 24 to 34 years of age

Results from the mixed linear regression model are reported in Table 3. There were no significant interactions with age by group in the unadjusted and adjusted mixed effects analyses; i.e. development over the complete age span did not differ between the EP and term-born group. Thus, the results from the analyses without

Table 1 Characteristics of 45 extremely preterm subjects, with or without disability, and 46 term-born controls who were born in 1982–1985 in western Norway[a]

	EP-born severe disability	EP-born healthy	Term-born controls	p-value[b]	p-value[c]
Birth characteristics	n = 8	n = 37	n = 46	–	–
Male, *n (%)*	5 (62.5)	22 (55.0)	26 (56.5)	1.000	0.826
Gestational age, weeks, *mean (SD)*	26.9 (2.0)	27.5 (1.7)	–	–	–
Birth weight, grams, *mean (SD)*	917 (164)	1017 (194)	3441 (311)	< 0.001	< 0.001
Age first follow-up, year, *mean (SD)*	17.1 (1.6)	17.1 (1.1)	17.4 (1.3)	0.711	0.318
Age 2nd follow-up, year, *mean (SD)*	24.3 (1.7)	24.2 (1.2)	24.6 (1.3)	0.546	0.111
Age 3rd follow-up, year, *mean (SD)*	34.7 (1.6)	34.2 (1.3)	34.4 (1.3)	0.706	0.656
BPD moderate/severe, *n (%)*	2 (15.4)	11 (84.6)	0	–	–
Neurosensory impairments, n (%)					
Disabling CP, *n (%)*	4 (50.0)	0	0	–	–
Non-disabling CP, *n (%)*	2 (25.0)	4 (10.3)	0	–	–
Deaf, *n (%)*	2 (25.0)	0	0	–	–
Blind, *n (%)*	2 (25.0)	0	0	–	–
Characteristics at 34 years follow-up	n = 6	n = 28	n = 36		
Highest educational attainment, n (%)				0.395	0.436
College/University, ≤ 4 years	5 (83.3)	20 (71.4)	22 (61.1)		
College/University, > 4 years	1 (16.7)	8 (28.6)	14 (38.9)		
Employment, n (%)				0.007	0.159
Working or still in education	3 (50.0)	24 (85.7)	35 (97.2)		
Unemployed or disability pension	3 (50.0)	4 (14.3)	1 (2.8)		
Martial status 34 years, n (%)				< 0.001	0.112
Single	6 (100)	8 (28.6)	4 (11.4)		
Married/cohabitant	0	20 (71.4)	31 (88.6)		
Having children, n (%)	0	17 (61.0)	25 (69.0)	0.002	0.002

BPD bronchopulmonary dysplasia *CP* cerebral paresis *EP* extremely preterm *SD* standard deviation;

[a] Information were obtained from a general questionnaire and medical chart

[b] EP-born severe disability vs. term-born controls

[c] EP-born healthy vs. term-born controls

Differences were tested using Welch's t-test for continuous variables and Fisher's Exact Test for categorical variables

the interaction term were reported. Figure 2 illustrates the similar reporting of four domains at 24 and 34 years for EP and term-born participants.

In the unadjusted mixed effects analyses, there were statistical significant differences between the EP-born and term-born participants over the ten years age span in seven of the eight domains (physical functioning, bodily pain, general health, vitality, social functioning, role emotional, and mental health). Adjusted for gender, education and employment status, the group differences remained, with EP-born scoring statistical significantly lower in vitality, social functioning, role emotional, and mental health.

Developmental of subjective health complaints from 17 to 34 years of age

Results from the mixed linear regression model are reported in Table 4. For somatic complaints, the adjusted mean estimated difference between EP-born and term-born participants was 0.76, but not significant, and this difference remained stable over the age groups (test for interaction p = 0.321), although it was numerically lowest at 17 years and highest at 24 years. The same pattern was shown for psychological complaints, but in this case the variation between the ages was statistical significant (interaction p = 0.027) with adjusted mean estimated differences of 0.00, 2.53 and 1.86 at 17, 24 and 34 years, respectively. The patterns for the two sub-scores are depicted in Fig. 3. The total score followed the same pattern, but the interaction was not significant (p = 0.058).

Discussion

In this population-based longitudinal study, HRQoL and subjective health complaints were repeatedly assessed from 17 to 34 years of age in EP-born adults and compared with a matched term-born control group. HRQoL

Table 2 Self-reported functional health and well-being, and Subjective health complaints at 34-years of age in 35 subjects born extremely preterm, with or without severe disability, and 35 matched term-born controls using the SF-36 questionnaire[a] and HBSC-SCL[c]

	EP-born severe disability (n = 6)		**EP-born healthy (n = 29)**		**Term-born controls (n = 35)**		**EP-born severe disability vs Term-born controls (n = 5)[b]**	**EP-born healthy vs Term-born controls (n = 19)[b]**
	Mean (SD)	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	**Mean difference with 95% CI**	**Mean difference with 95% CI**
SF-36 domains								
Physical Functioning	55.0 (41.1)	5–100	92.8 (9.6)	65–100	94.4 (11.0)	50–100	-55.0 (-112.0, 2.0)	-2.4 (-9.4, 4.7)
Role Physical	66.7 (51.7)	0–100	87.9 (29.6)	0–100	85.7 (32.8)	0–100	-40.0 (-108.0, 28.0)	1.3 (-19.0, 21.6)
Bodily Pain	63.0 (35.2)	22–100	74.8 (26.0)	22–100	78.5 (22.9)	22–100	-30.4 (-72.5, 11.7)	-9.9 (-26.7, 6.9)
General Health	51.6 (28.3)	25–87	69.9 (21.7)	20–100	75.7 (18.7)	25–100	-25.5 (-56.4, 5.4)	-11.1 (-24.1, 1.9)
Vitality	31.9 (20.6)	5–55	50.5 (21.7)	0–85	60.3 (19.1)	5–85	-15.7 (-20.4, 10.9)	**-19.2 (-35.0, -3.3)**
Social Functioning	72.9 (21.5)	50–100	81.5 (30.2)	0–100	89.6 (22.6)	0–100	-20.0 (-50.2, 10.2)	-17.1 (-37.1, 2.9)
Role Emotional	50.0 (54.8)	0–100	75.9 (38.7)	0–100	91.4 (26.0)	0–100	-40.0 (-108.0, 28.0)	**-22.8 (-45.6, -0.1)**
Mental Health	57.3 (24.9)	16–84	76.0 (17.2)	16–96	79.9 (16.7)	16–92	**-17.6 (-35.1, -0.2)**	**-10.4 (-20.9, 0.0)**
HBSC-SCL variables[c]								
HBSC total (0–32)	8.0 (8.2)	0–21	7.5 (7.8)	0–32	5.3 (6.1)	0–25	-0.3 (-5.9, 5.5)	**5.6 (0.6, 10.7)**
Somatic complaints, sub-score (0–16)	2.6 (2.9)	0–7	3.3 (4.1)	0–16	2.5 (2.8)	0–9	0.3 (-3.9, 4.4)	2.2 (-0.4, 4.8)
Psychological complaints, sub-score (0–16)	5.4 (5.6)	0–14	4.2 (4.6)	0–16	2.6 (3.7)	0–16	-0.5 (-2.6, 1.6)	**3.4 (0.6, 6.3)**

CI confidence interval *EP* extremely preterm *HBSC* Health Behaviour in School-aged Children-Symptom Checklist *SD* standard deviation

Bold results: $p \leq 0.05$

[a] SF-36 (Short Form Health Survey-36), with possible domain scores from 0 to 100, higher score indicates better functional health and well-being

[b] The lower number is due to missing in pairs

[c] Higher score indicates more symptoms

Table 3 Pooled data of self-reported functional health and well-being at 24 and 34 year of age in subjects born extremely preterm and age- and gender matched term-born controls using the SF-36 questionnaire[a]

	Unadjusted[b] Mean difference	**Adjusted[c] Mean difference**
Response variable SF-36	EP-born verus Term-born estimate with 95% CI	EP-born versus Term-born estimate with 95% CI
Physical Functioning	−8.93 (−14.56, −3.30)**	−1.60 (−7.18, 3.98)
Role Physical	−5.54 (−15.11, 4.02)	−0.98 (−11.00, 9.04)
Bodily Pain	−8.80 (−16.48, −1.13)**	−2.81 (−11.13, 5.50)
General Health	−7.23 (−13.08, −1.39)**	−5.94 (−13.19, 1.31)
Vitality	−11.15 (−16.84, −5.47)***	−7.34 (−14.08, −0,61)*
Social Functioning	−11.97 (−19.55, −4.40)**	−10.11 (−18.10, −2.12)*
Role Emotional	−22.11 (−33.19, 11.04)***	−15.48 (−27.40, −3.55)**
Mental Health	−8.83 (−13.86, −3.79)***	−6.12 (−11.87, −0.36)*

CI confidence interval *EP* extremely preterm *SD* standard deviation

[*] $p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$

[a] SF-36: Short Form Health Survey-36, with possible domain scores from 0 to 100, higher score indicates better functional health and well-being

[b] Mixed effects linear models including EP-born and term-born and age group. No significant difference between age 24 and 34 was found and therefore the results without age in the model are reported to increase the statistical power

[c] Mixed effects linear models adjusted for gender, education level, employment status and age were used in the model to assess differences in the SF-36 scores between 24 and 34 years, and between the groups at each age, including a group by age interaction

[d] College/University under or over 4 years

[e] Not working/retirement income or working

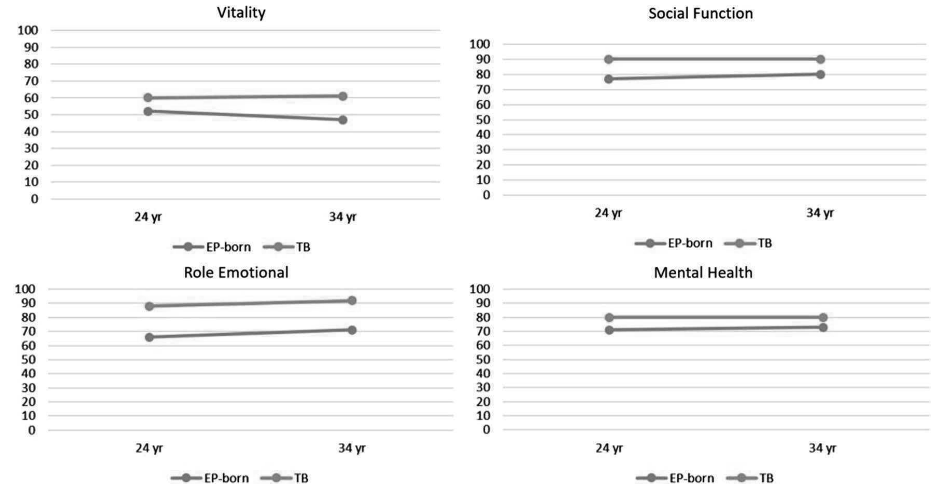

Fig. 2 Group means of four self-reported HRQoL domains from 24 to 34 years of age in the extremely preterm (EP) born and the term-born (TB) participants according to SF-36. Higher score indicates better HRQoL, possible score from 0 to 100

Table 4 Differences in subjective health complaints at 17, 24 and 34 years between subjects born extremely preterm, and matched[a] controls born at term provided by the Health Behaviour School-aged Children-Symptom Checklist (HBSC-SCL)[b] and estimated by mixed linear models[c]

	Unadjusted	**Adjusted**				
Response variable HBSC-SCL	**Mean difference EP-born versus Term-born Estimate 95% CI**	**At age 17 years Mean difference EP-born versus Term-born Estimate 95% CI**	**At age 24 years Mean difference EP-born versus Term-born Estimate 95% CI**	**At age 34 years Mean difference EP-born versus Term-born Estimate 95% CI**	**Group by age p-value**	**Mean difference EP-born versus Term-born Estimate 95% CI[d]**
Total score	2.21 (0.84, 3.59)**	0.22 (− 1.97, 2.40)	4.01 (1.68, 6.34)	2.85 (0.26, 5.44)	0.058	2.36 (0.62, 4.11)
Somatic complaints sub-score	0.85 (0.14, 1.55)**	0.22 (− 0.91, 1.34)	1.47 (0.27, 2.67)	0.97 (− 0.37, 2.31)	0.321	0.76 (− 0.15, 1.67)
Psychological complaints sub-score	1.37 (0.54, 2.19)***	0.00 (− 1.31, 1.31)	2.53 (1.14, 3.92)	1.86 (0.32, 3.40)	0.027*	1.63 (0.61, 2.65)

CI confidence interval *EP* extremely preterm *HBSC-SCL* Health Behaviour in School-aged Children-Symptom Checklist *SD* standard deviation

*$p \le 0.05$; **$p \le 0.01$; ***$p \le 0.001$

[a] Matched for gender and age

[b] With possible score from 0 to 32 on total HBSC and 0–16 on sub-scores. Higher score indicates more symptoms

[c] Mixed linear models were used to assess differences in the HBSC-SCL scores between the groups at each age 17, 24 and 34 years, by including a group by age interaction [d]Adjusted for gender, education level, employment status and age in models without group by age interaction

was poorer in EP-born without severe disabilities at 34 years, and their scores were unchanged from previous assessments at 24 years of age. EP-born also scored poorer regarding subjective health complaints at 34 years, but development from 24 years was positive (less complaints) for sub-scores addressing psychological issues. EP-born with severe disabilities were few, which prevented firm conclusions for this group.

HRQoL in the EP-born participants of this study was poorer at 34 years of age compared to matched term-born controls, and had remained unchanged over the age span covering the preceding decade from 24 to 34 years

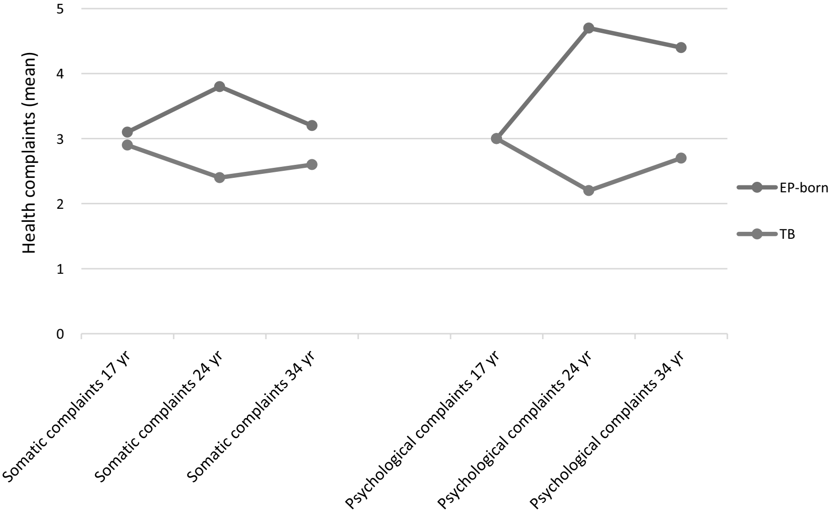

Fig. 3 Group means of self-reported somatic and psychological health complaints from 17 to 34 years of age in the extremely preterm (EP) born and the term-born (TB) participants according to the Health Behaviour in School-aged Children–Symptom Checklist (HBSC-SCL). Higher score indicates more complaints, possible sub score from 0 to 16 on sub scores

of age. The scores of the control group were in line with observations made in a large study covering a comparable background population, as was also their stable development during this same age span [31]. The scores for our EP-born were in agreement with the few longitudinal studies that have been carried out in preterm-born adults. Saigal et al. [23] found the same poor HRQoL scores over time, measured by the Health Utilities Index Mark 3 (HUI3), as did also a Dutch study which also applied the HUI3 during the period 19 to 28 years [22]. Our results are also in line with some cross-sectional studies from early adulthood [12, 34], although there are inconsistencies in the literature with some studies reporting similar HRQoL in preterm born and term-born peers [21, 35–37].

Causal relationships between EP birth and poor HRQoL cannot easily be extracted from this dataset, and we are left with speculations. In their mid-twenties, most young adults find themselves in a process of establishing an independent life, about to finish education, and/or in search of a job or future career. Later, in their mid-thirties, most will be in more permanent work and social arrangements, perhaps with children on their own. We found that by the age of 35 years, fewer EP-born than term-controls had established relationships with another person, their level of education was lower, and more were unemployed or received some kind of financial support. As such, they seemingly had achieved a different level of independent life than their term-born peers and these and all these sociodemographic factors are known to be related to poorer HRQoL [38–41]. However, the association between these variables are unknown, and poor HRQoL might represent both a cause and a consequence of a disadvantageous life situation. For example, some authors argue that level of education should be considered an outcome after preterm birth [42], whereas others disagree [43]. In our dataset, group differences in the mental health domains remained in analyses adjusted for educational level and employment status, indicating that these deficits could not be explained by these factors alone.

EP-born with severe disabilities were rare in our cohort, which prevented firm conclusions for this group; however, their scores were numerically poorer for all HRQoL domains when compared with the control group as well as the EP-born without severe disabilities. For healthy EP-born, poor HRQoL scores were particularly evident on the domains addressing vitality, role emotion and mental health. These domains reflect experiences of depression, difficulties at work or in social contexts due to emotional problems, and feelings of fatigue. Decreases versus the control group were not only of statistical significance; they also exceeded levels regarded clinically significant [29], and therefore likely to be of major personal importance for those affected. As HRQoL represent a fundamental measure of health [18] these findings are also of obvious societal interest, given the high number of EP-born currently entering adulthood [44]. Thus, it is vitally important to understand what may contribute to this situation.

Contrasting HRQoL, development from 24 to 34 years regarding health complaints was positive (less complaints) in our EP-born group. One way of interpreting the development from 24 to 34 years is by a shift in internal standards and how questions are valued; a mechanism referred to as response shift [45]. This would imply that EP-born well into adulthood live better with complaints they had also as young adults at 24 years. If that is correct, this mechanism has come into play only for psychological complaints, not for somatic complaints and also not for HRQoL. We argue that this is a phenomenon that should be considered and investigated also in EP-born populations, as it has been studied in patients with severe chronic conditions and cancer patients [46].

The major strengths of this study were the longitudinal design that takes us well into adulthood, participation of the same matched term-born control group throughout the complete study period, a relatively high participation rate, and the use of standardised and validated questionnaires. Recruitment of the term-born control group was based on the 'next born subject principle', minimising the risk of selection bias. There were rather wide confidence intervals on the different HRQoL domains, irrespective of disabilities or not, suggesting that our EP-born participants were rather heterogeneous. This may challenge the generalisability, but may also be viewed as reflections of heterogeneous outcomes after EP birth and thus traits to be expected in studies like the present. A relatively small overall sample size decreased statistical power, challenged inclusion of possible confounding variables, and increased the risk of type-two errors, particularly relevant to the comparisons between EP-born with and without severe disability. The study was part of an extensive follow-up investigating a range of variables after EP birth, and power calculations had been done 20 years ago focusing on lung function. Post hoc power calculations were not carried out [47], and instead we provide 95% confidence intervals and p-values to quantify the uncertainty. Another limitation is that RAND-36 was used at the second follow-up, compared to SF-36 at the first. As mentioned in the Methods section, RAND-36 is considered equivalent to the SF-36, and we do not believe this had an impact on our results, but important to have in mind.

Our participants were born in the early 1980s and represent a "pioneer generation" in the sense that most infants born at this early stage during preceding decades had died. Survival rates have increased since the 1980s, particularly in the low gestational age range, and increasingly more survivors of extreme immaturity are currently approaching adulthood. Thus, we need sufficiently powered follow-up studies to explore potential cohort effects, and we should conduct in-depth qualitative studies to investigate the lived experience of EP-born individuals. The longitudinal data provided in this present study suggest there may be a window of opportunity during their late teens with advantageous self-reported scores for quality of life and health complaints that perhaps can be utilized for interventions.

Conclusion

The study demonstrates that 34-years-old EP-born adults had poorer HRQoL than term-born peers, especially in the mental health domains, and that these deficits had remained unchanged during the preceding decade. Thus, one may fear that this situation may endure even further with unknown consequences. Similarly, healthy 34-year-old EP-born with no major disabilities had more subjective health complaints compared to term-born peers; however, development during the preceding decade had improved for the psychological subscale, suggesting either real improvement or some sort of shift in internal standards on how questions are valued.

Abbreviations

EP: Extremely preterm; NICU: Neonatal intensive care unit; GA: Gestational age; BW: Low birthweight; HRQoL: Health-related quality of life; SF-36: Short-Form Health Survey; HBSC-SCL: Health behaviour in school-aged children-symptom check list; SD: Standard deviation; CP: Cerebral palsy; BPD: Bronchopulmonary dysplasia; HUI3: Health utilities index mark 3.

Acknowledgements

We thank the participants for their generosity in participating in our ongoing study for many years.

Author contributions

MB collected and analysed the data, drafted the initial manuscript, reviewed and edited the manuscript. MV collected the data. BV, MV and TH decided on the data collection tools. BV, JD, MV and TH reviewed and edited the manuscript. GEE analysed the data, and reviewed and edited the manuscript. All the authors approved the final manuscript as submitted. All authors read and approved the final manuscript.

Funding

Open access funding provided by University of Bergen. No funding was received for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The Western Norway Regional Health Authority and the Norway's Research Council supported this study.

Availability of data and materials

In accordance with the approvals granted for this study by The Regional Committee on Medical Research Ethics, the data files are stored securely and in accordance with the Norwegian Law of Privacy Protection. The data file cannot be made publicly available as this might compromise the respondents' privacy. A subset of the data file with anonymized data can be made available to interested researchers upon reasonable request to Thomas Halvorsen (thomas.halvorsen@helse-bergen.no), providing Norwegian privacy legislation and GDPR are respected, and that permission is granted from The Norwegian

Data Inspectorate and the data protection officer at Haukeland University Hospital.

Declarations

Ethics approval and consent to participate

The Regional Committee for Medical Research Ethics for Western Norway approved the study protocol (Protocool no. 2017/628). Informed consent was obtained from all individual participants included in the study.

Consent for publication

Participants signed informed consent regarding publishing their data.

Competing interests

The authors declare that they have no competing interests.

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Received: 20 August 2021 Accepted: 10 July 2022
Published online: 23 July 2022

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Publisher's Note

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Early Human Development 173 (2022) 105661

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Long-term follow-up of self-reported mental health and health-related quality of life in adults born extremely preterm

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ARTICLE INFO

Keywords:
Extremely premature infant
Mental health
RAND-36
Preterm adults
Long-term outcome
Quality of life
Cohort studies
Self-report
Anxiety

ABSTRACT

Background: Survival of extremely preterm (EP) birth is increasing, but long-term consequences are still largely unknown as their high survival rates are recent achievements.
Aims: To examine self-reported mental health, and health related quality of life (HRQoL) in a cohort of adults born EP in the early 1990s and individually matched term-born controls, and to describe development through the transition from teenager to adults.
Methods: Thirty-five eligible subjects were born at gestational age $\leq$ 28 weeks or with birth weight $\leq$ 1000 g during 1991–1992 in this population-based cohort from Western Norway. We assessed mental health using Youth Self-Report (YSR) at 18 years of age, and Adult Self-Report (ASR) at 27 years, and HRQoL by RAND-36 at 27 years. Data were analysed by unadjusted and adjusted mixed effects models with time by group as interaction term.
Results: At 27 years, 24 (69 %) EP-born and 26 (74 %) term-born controls participated. Scores for internalising problems, and syndrome scale anxious/depressed and withdrawn were higher among EP-born compared to term-born controls. For HRQoL, scores were similar in EP-born and term-born groups, except the domain physical functioning where EP-born scored lower. Development over time from 18 to 27 years showed increasing (i.e. deteriorating) scores for internalising, anxious/depressed, somatic complaints, and attention problems in the EP born group. For the term-born, scores for anxious/depression increased over time.
Conclusions: At 27 years of age, EP-born adults reported more internalising problems than term-born controls, while HRQoL was relatively similar except physical functioning. Mental health problems in the EP-born increased from adolescence to adulthood.

1. Introduction

More children born extremely preterm (EP) now survive due to vast improvements of perinatal care over the last decades, particularly to the benefit of those born most immature [1]. EP-born children now constitute nearly 1 in 200 individuals growing up in high income societies [2]. Survival of these infants implies that growth and development must take place in a neonatal intensive care unit (NICU) while receiving comprehensive and invasive lifesaving treatments; a demanding and even harmful scenario to the infants themselves as well as their parents. Preterm birth has long-lasting and possible life-long health effects with increased risk of a variety of impairments across the lifespan [3]. Thus, adolescents and young adults born EP have been found to be at increased risk of cognitive and social limitations, neurological deficiencies, mental health problems, metabolic disorders, respiratory disorders, and pulmonary and cardiovascular abnormalities [4]. Further, reduced educational qualifications and employment rates, and increased prevalence of social benefits have been found in EP-born adult populations [5,6]. In

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Abbreviations: GA, gestational age; EP, extremely preterm; YSR, Youth Self-Report; ASR, Adult Self-Report; HRQoL, Health-related Quality of Life; VP, very preterm; VLBW, very low birthweight; BW, birthweight; TB, term-born; NICU, neonatal intensive care unit; ADM, assessment data manager.

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https://doi.org/10.1016/j.earlhumdev.2022.105661
Received 13 June 2022; Received in revised form 23 August 2022; Accepted 24 August 2022
Available online 31 August 2022
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this context, subjective health, mental health, and health-related quality of life (HRQoL) are highly relevant issues. These measures are still not well described, particularly development throughout the important transitional phase from adolescence to adulthood [7].

The risk of mental health problems in preterm born adults is not fully understood. A meta-analysis from 2017 [8] reported that young adults born very preterm suffered from more internalising and antisocial problems, whereas externalising problems seemed less prevalent than in term-controls. A recent Norwegian study found higher levels of problems relating to attention, internalising and externalising issues at 26 years of age in subjects born with very low birthweight (VLBW) when compared to matched controls [9]. Particularly anxiety and depression seem to be areas of concern in preterm born [10,11]. However, the literature is not consistent, with conflicting data [10,11]. A systematic review from 2020 concluded that it remains undetermined whether VLBW/ EP adults are at increased risk of mental health disorders or symptoms [12]. Further, studies are few, particularly with a longitudinal design, which is pivotal to the understanding of developmental trends over time. Mental health is closely related to HRQoL, which examines the relationship between an individual's health and ability to function, and the perception of well-being [13]. HRQoL is multidimensional and includes physical, social and psychological functioning [14]. A recent systematic review could not conclude if HRQoL differed between adults born VLBW and at term [7].

In a cohort born EP in the early 1980s, we found that HRQoL deteriorated from 18 to 24 years of age, with scores below those of term-born controls at 24 [15]. In a cohort born similarly preterm in the early 1990s, we found that HRQoL and self-reported mental health did not differ from term-born controls at 18 years [16]. With this present study, we report new data from the 1990-cohort and their term-born controls, aiming to (1) investigate HRQoL and self-reported mental health a decade later, and (2) investigate longitudinal development during the age-span from 18 to 27 years.

2. Methods

2.1. Study design and participants

Longitudinal population-based follow-up study, enrolling adults born at GA $\leq$ 28 weeks or with BW $\leq$ 1000 g in 1991–1992 within a defined area in Western Norway. At the age of ten, eligible children were retrospectively identified through the admission protocols at the NICU at Haukeland University Hospital, Bergen Norway, which is the only hospital in the region which cares for infants born extremely premature. All infants born at GA $\leq$ 28 weeks or with BW $\leq$ 1000 g who were admitted alive to the NICU were considered eligible. Of 47 admitted infants, 12 (26 %) died, leaving 35 eligible subjects who all responded positively and provided consent to participate at first follow-up in 2001–2002. Neonatal morbidity data are presented in Table 1. This was the third examination of this cohort, performed at age 27 during 2018–2020.

Term-born controls, individually matched for each EP-born participant, had been recruited at 10 years of age. The temporally nearest term-born child of the same gender with BW between three and four kilograms (Norwegian 10th to 90th percentile) was approached. If the parents of that person declined, the following term-born subject was approached, and so on until one control had been recruited for each enrolled EP-born participant.

Assessments were performed at Haukeland University Hospital at 10 years of age (first follow-up, not described here), 18 years (second follow-up), and 27 years (third follow-up).

2.2. Measures

Table 1
Clinical characteristics, neonatal morbidity and demographics at 27 years follow-up of 24 participants born extremely preterm in Western Norway and their 26 term-born controls.[a]

	EP-born	Term-born controls	*p*-Value
	n = 24	*n* = 26	
Birth characteristics			
Male, *n (%)*[d]	10 (42)	8 (31)	0.42
Age at second follow-up, year, *mean (SD)*	17.7 (0.4)	17.9 (0.5)	–
Gestational age at birth, weeks, *mean (SD)*	26.7 (1.7)	–	–
Birthweight, grams, *mean (SD)*[b]	944 (224)	3,540 (270)	<0.001
Days on ventilator, *mean (SD)*	10.0 (13.4)	0	–
Days on oxygen treatment, *mean (SD)*	61.8 (51.5)	0	–
Bronchopulmonary dysplasia (BPD[c])	9 (38)	0	–
Intra-ventricular haemorrhage grade 1–2[d], *n (%)*	7 (29)	0	–
Necrotising enterocolitis	3 (13)		–
Retinopathy of prematurity	0 (0)		–
Patent ductus arteriosus, surgical closure, *n (%)*	13 (54)		–
Characteristics at 27 years' follow-up			
Cerebral Palsy, *n (%)*	0 (0)		–
Impaired hearing, *n (%)*	2 (8)		–
Reduced vision, *n (%)*	2 (8)		–
Age at third follow-up, year, *mean (SD)*[b]	26.6 (0.7)	26.6 (0.6)	0.96
College/university $\leq$4 years[d]	19 (79)	18 (69)	0.42
College/university >4 years	5 (21)	8 (31)	
Employment, n (%)			
Working or still in education[d]	18 (75)	26 (100)	0.007
Unemployed or disability pension	6 (25)	0 (0)	

EP = extremely preterm; SD = standard deviation.

[a] All information about demographic and clinical characteristics were obtained from a general questionnaire and medical chart. The subjects were born 1991–1992.

[b] Comparison between groups using Welch's *t*-test.

[c] BPD defined by oxygen supply and/or ventilator support at gestational age 36 weeks.

[d] None grade 3–4.

At this third follow-up, the participants completed questions covering socio-demographic data, self-report on mental health and quality of life, the same issues as at the follow-up at age 18. Results from the first two follow-ups have been published previously [16].

2.3. Socio-demographic and clinical data

Information on socio-demographic data, such as current educational level and employment, were obtained from a custom-made questionnaire used in Norwegian population studies (http://www.hunt.ntnu.no). Educational level five-point response choices were from (1) elementary school through (5) college/university exceeding 4 years; for the purpose of statistical analyses later dichotomized to 1–4 versus 5. Employment four-point response choices were (1) working, (2) student, (3) unemployed or (4) disability pension, later dichotomized to 1–2 versus 3–4. Clinical data were obtained from the participants themselves and from hospital records.

2.4. Self-reported mental health; Youth Self-Report (YSR) and Adult Self-Report (ASR)

Behavioral, emotional, and social difficulties were measured using Norwegian validated versions of Youth Self-Report (YSR) at 18 years and Adult Self-Report (ASR) at 27 years [17,18]. Correlation between YSR and ASR is found to be stable and acceptable in American and Dutch samples [19,20]. These questionnaires comprise 118 (YSR) and 120 (ASR) behavioral, emotional, and social problem items rated as "not true" (0), "somewhat or sometimes true" (1), or "very true or often true" (2), based on the last 6 months. A sum score was calculated for each syndrome scale. Six of these sum scores are used to create two broadband scales: an *internalising score* (anxious/depressed, withdrawn and somatic complaints) and *externalising score* (rule-breaking behaviour, aggressive behaviour (and intrusive behaviour only in the ASR)). The *total score*, based on all problem items (including thought and attention problems (and social problems in the YSR)) represents the total problems score. Higher scores indicate more problems and poorer functioning.

These questionnaires are widely used measures of social-adaptive and psychological functioning in youth aged 11–18 [17] and adults aged 18–59 [21], and it is recommended measures in follow-up assessments of adults born preterm [22].

2.5. RAND 36-Item Health Survey (RAND-36)

HRQoL was measured by RAND-36 at age 27, a questionnaire developed by the RAND Corporation [23]. RAND-36 is equivalent to the 36-item SF-36, except minor differences in the scoring procedure for the two sub-scales of general health and pain which are slightly different, and the RAND-36 scores correlate highly (0.99) with the SF-36 scores [24]. It is a generic measure assessing self-perceived functional health and well-being through the following eight health domains: physical functioning (ten 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, which have dichotomized response choices, the responses are rated along a three to six-point ordinal scale with the preceding four weeks as the recall period, except for physical functioning and general health, which pertain to the current status. The raw scores for each RAND-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 score from 0 to 100, with higher scores indicating better functional health and well-being [13,23]. The questionnaire has demonstrated good reliability and validity [23], including in Norwegian populations [25]. Term-born controls were expected to represent the general population, and they were in line with normative Norwegian data [25] except for physical functioning and role physical, where the term-born scored 3 points higher compared to normative data.

2.6. Statistical analysis

Descriptive statistics are reported as mean with standard deviations (SDs). The statistical analyses were performed in three stages. First, we compared characteristics of the participating and non-participating eligible subjects using Welch's *t*-test and Person Chi-square, to discover potential selection bias. Secondly, we used assessment data manager (ADM) scoring software, and transformed raw data of YSR and ASR to SPSS. We then used Welch's *t*-test to examine characteristics and HRQoL differences between EP-born and term-born controls. Approximate normal distribution of scores in each group was assessed by visual inspection of Q-Q plots. Thirdly, to estimate longitudinal differences in mental health (YSR and ASR), we fitted linear longitudinal regression models with group (EP-born vs. term-born), age (18 vs. 27 years) and the group–age interaction as explanatory variables. For each individual, the two error terms (at ages 18 and 27) were modelled as correlated. The use of a longitudinal model with correlated error terms allowed us to include subjects with only partial follow-up data, which should reduce the effect of bias from missing data. There were some missing data, especially at the follow-up at 27 years. We report the number of patients each analysis is based on.

Since there were large differences in SDs, both between the two groups and between the two time-points, we used heteroscedastic error terms (different SDs for the four group–age combinations). We also fitted a similar model with gender as an additional predictor.

A *p*-value <0.05 is characterised as statistically significant, and 95 % confidence intervals (CI) are reported where relevant. For data analyses with Welch's *t*-test and Pearson Chi-square, the SPSS statistical package version 26 was used. The regression models were fitted using the 'nlme' package version 3.1-153 [26] in R version 4.1.1 [27].

2.7. Ethics

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

3. Results

3.1. Clinical characteristics

At 27 years, 23 (66 %) EP-born and 26 (74 %) term-born controls participated (Fig. 1). Clinical and sociodemographic characteristics are shown in Table 1. The mean age at the last follow-up was 26.6 years for both EP-born and term-born controls. There were no significant differences in gender or educational attainment between EP-born and term-born controls, but six of the EP-born participants were unemployed or on disability pension, compared to none in the term-born group ($p = 0.01$).

3.2. Participants vs. non-participants

There were no significant differences with regard to BW, GA, or days on ventilator between EP-born participants and those who did not participate. Also, between term-born participants and those who did not participate, no significant differences were found on gender and BW. Further characteristics are presented in Additional file 1: Table S1 and S2.

3.3. Self-reported mental health at 27 years; data from ASR

At 27 years, the scores for total problems, the broadband internalising problems, and the two syndrome scales "anxious/depressed" and "withdrawn" were significantly higher (i.e. more problems) in the EP-born group (Table 2). Three EP-born participants did not complete the ASR.

3.4. Health-related quality of life at 27 years; data from RAND-36

EP-born scored significantly lower than term-born on physical functioning, whereas scores were similar in the remaining 7 domains (Table 3).

3.5. Changes of self-reported mental health (YSR and ASR) from 18 to 27 years in EP-born and term-born

Longitudinal data are depicted in Table 4 and visualised in Fig. 2. In the EP-born group, scores increased over time for the broadband internalising, and syndrome scale anxious/depressed, somatic complaints and attention problems, indicating more mental health problems. Further, scores declined over time for aggressive behaviour and rule-breaking behaviour in the EP-born group, indicating less problems.

In the term-born group, scores for anxious/depression increased over time, whereas scores were declining for broadband externalising problems, and syndrome scale aggressive behaviour and rule-breaking behaviour.

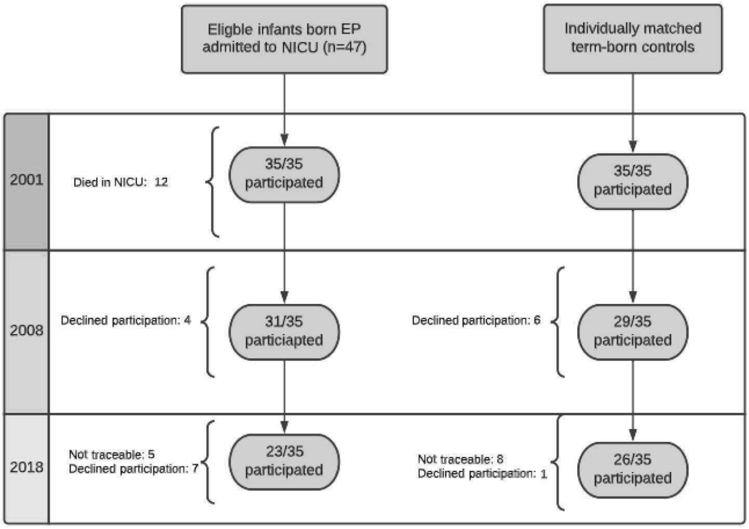

Fig. 1. Flow chart of the 35 extremely preterm (EP) born subjects and 35 matched term-born controls at the three follow-up time points. EP Extremely preterm, NICU neonatal intensive care unit.

Table 2
Self-report at 27 years of age in subjects born extremely preterm and term-born controls by Adult Self-Report (ASR).

ASR	EP-born (n = 21)[a]		Term-born controls (n = 26)		EP-born vs. term-born controls			
	Mean	SD	Mean	SD	Estimated mean difference	Lower CI	Upper CI	p-Value
Raw scores								
Anxious/depressed	10.5	7.7	5.6	5.5	4.9	1.2	8.6	0.01
Withdrawn	3.6	3.2	1.7	1.6	1.8	0.4	3.3	0.02
Somatic complaints	3.8	3.5	3.0	2.8	0.8	−1.1	2.7	0.41
Thought problems	2.2	2.5	1.2	1.5	1.0	−0.2	2.2	0.12
Attention problems	7.6	5.7	5.4	4.2	2.2	−0.6	4.9	0.12
Aggressive behaviour	3.9	4.1	2.1	1.9	1.8	−0.1	3.7	0.07
Rule-breaking behaviour	1.6	1.9	0.9	1.3	0.7	−0.3	1.6	0.17
Internalising problems	17.6	11.6	10.3	8.3	7.2	1.5	12.9	0.01
Externalising problems	6.8	5.6	4.7	3.2	2.1	−0.6	4.8	0.12
Total problems	43.3	28.0	28.4	18.9	14.8	1.3	28.3	0.03

EP = extremely preterm; SD = standard deviation; CI = confidence interval.
Raw scores are given for all scales. Higher scores indicate more problems.
Analysed performed with linear longitudinal regression models.
[a] Data missing for 3 EP-born.

3.6. *Changes over time for self-reported mental health (YSR and ASR) compared for EP-born vs. term-born controls*

As visualised in Fig. 2, the trend on all syndrome scales indicated that the EP-born group reported more problems compared to term-born controls, with significantly more broadband externalising problems and on the syndrome scale of anxious/depressed problems. Only minimal effects were found when adjusting for gender differences (data not shown).

4. Discussion

Adults born EP in the early 1990sreported more mental problems than term-born controls at 27 years of age, particularly internalising problems, and problems were increasing during the period from 18 to 27 years, specifically issues relating to anxiety and depression. The EP-born group scored poorer than term-born on the HRQoL domain physical functioning, whereas scores for the remaining seven domains were similar.

Our finding of more mental health problems in EP-born, particularly internalising problems, are in line with a meta-analysis from 2017 based on six cohorts of adults born VLBW [8], and a review by Mathewson et al. [28], both indicating more depression and anxiety in adults born ELBW. Internalising problems incorporate problems within the self, such as anxiety, depression and withdrawal from social interactions [19]. Interestingly, anxiety has been suggested to characterise the preterm born behavioral phenotype [29], which our results certainly support. The book *Preemie Voices* by Saroj Saigal, with personal narratives told by EP-born adults, highlights anxiety as a common concern [30].

It is of concern that 25 % of our EP-born participants were either unemployed or received disability benefits, compared to none in the term-born control group. This is in line with the findings of a meta-analysis reporting on unemployment rates in EP-born populations [5]. Interestingly, a European longitudinal study, reporting on data from the general population, found that depressive symptoms were associated with risk of unemployment [31]. We do not know if these features are

Table 3
Self-reported functional health and well-being at 27-years of age in 24 subjects born EP, and 24 matched term-born controls using the RAND-36 questionnaire[a].

RAND-36 domains	EP-born (n = 24)		Term-born controls (n = 25)		EP-born vs. term-born controls	
	Mean	SD	Mean	SD	Mean difference with 95 % CI	p-Value[b]
Physical functioning	93.1	8.6	98.0	4.8	−5.0 (−9.1, −0.8)	0.02
Role physical	84.8	29.9	92.0	17.3	−7.2 (−21.7, 7.3)	0.32
Bodily pain	80.7	19.8	86.9	18.9	−6.3 (−17.5, 5.0.8)	0.27
General health	68.5	21.8	75.6	21.5	−6.3 (−19.7, 5.5)	0.26
Vitality[c]	61.0	21.5	63.2	20.5	−2.3 (−14.7, 10.1)	0.71
Social functioning	78.8	27.3	88.0	18.6	−9.2 (−23.0, 4.6)	0.18
Role emotional	79.7	29.7	86.7	30.4	−7.0 (−24.4, 10.5)	0.43
Mental health[c]	75.6	16.0	78.9	18.7	−3.2 (−13.4, 7.0)	0.52

CI = confidence interval; EP = extremely preterm; SD = standard deviation.

[a] RAND-36, with possible domain scores from 0 to 100, where higher scores indicate better functional health and well-being.

[b] Analyses performed with Welch's *t*-test.

[c] Data missing for one EP-born.

causally related, and if they are, in which direction the relationship works; however, targeting depressive symptoms in EP-born populations will nonetheless contribute to a reduced burden of disease and social disadvantage. Gender has also been linked to mental health with more internalising problems for females [32], this was not the case in our study. This same lack of effect from gender was found also in another Norwegian low-birthweight study [33], but contrasts others which report more depression and anxiety in women born VLBW [34].

A better understanding of modifiable factors that may affect an increased risk of mental health problems linked to preterm birth is important, as it may point out avenues for intervention. Several studies have looked into this. Saigals group in Canada found that maternal anxiety disorder was associated with more internalising problems in adult offspring born ELBW [35]. Another study found high afternoon cortisol levels in EP-born adults, which led the authors to suggest that the neuroendocrine system may affect the development of psychopathology [36]. Yet another study pointed out gene–environment interactions that predicted internalising problems in the third and fourth decades of life [37]. Finally, a forth study suggested that smaller cerebellar volume in young adults born VLBW may be a biomarker of increased risk of psychiatric problems [38]. These findings and hypotheses may all represent possible associations that are involved in causal chains leading to internalising problems in preterm born adults, as observed in or our cohort. However, the scant volume of literature, as well as a tendency for arguments being built on somewhat weak evidence, display our lack of understanding of these issues, and the need for more research.

Developmental trends should be described in order to properly appreciate the life-long impact of preterm birth, with the transition from being a teenager living at home to independent adult life being particularly important. Most studies addressing this subject are done in groups born at very low birthweight; i.e. born more mature than the participants of the present study. We found that mental health problems increased from 18 to 27 years, in line with a Norwegian cohort born VLBW in the 1980s, reporting increasing mental health problems from adolescence to young adulthood [39]. A Canadian study [40] investigating a group born VLBW in the 1980s, found that internalising problems persisted in preterm born but decreased in term-born. These studies based on self-reports are supported by a study where depression and anxiety were diagnosed by interviews [41], as well as by a study suggesting that psychiatric hospital admissions increased with the degree of preterm birth [42]. A meta-analysis found higher odds for ASD, ADHD, anxiety disorder and Mood Disorders in adults born very preterm or at VLBW compared to controls born at term [43], and a systematic review found increased risk of use of any psychotropic medication in adults born very preterm or with VLBW during 1977–1995 [12].

Having a mental disorder while growing up is a potent risk factor for psychiatric problems later in life, but early interventions to ameliorate distress and access to treatment can reduce this risk [44]. EP-born children tend to be followed systematically only during their first few years of life [45], in Norway until the age of five years [46]. Our and other's findings pinpoint that preterm-born adults are at increased risk of mental and psychiatric problems, making surveillance and early interventions highly relevant in this group. This supports the cost-effectiveness of systematic follow-up of preterm born individuals, extending beyond early childhood, in line with suggestions proposed in a recent review [47]. The authors advocate a paradigm shift toward proactive interventions in this high risk group, rather than the reactive practice of waiting for aberrant tendencies becoming apparent.

Regarding HRQoL, the outcomes were good in all domains except physical functioning, which is in line with a recent study of young adults born VLBW in Canada [48]. Importantly, both the term-born and EP-born groups scored in line with normative data of the Norwegian

Table 4
Estimated changes from 18 to 27 years in scores of Youth Self-Report (YSR) and Adult Self-Report (ASR).

	EP-born (n = 33)[a]				Term-born controls (n = 32)[b]				EP-born vs. term-born controls			
	Estimate[c]	Lower CI	Upper CI	p-Value	Estimate[c]	Lower CI	Upper CI	p-Value	Estimate	Lower CI	Upper CI	p-Value
Raw scores												
Anxious/depressed	5.4	2.9	8.0	<0.001	2.4	0.8	4.1	0.005	3.0	0.0	6.0	0.05
Withdrawn	0.1	−1.2	1.4	0.85	−0.7	−1.5	0.1	0.08	0.8	−0.7	2.3	0.27
Somatic complaints	1.8	0.0	3.6	0.05	0.4	−1.0	1.8	0.54	1.4	−0.8	3.6	0.21
Thought problems	−1.0	−2.6	0.6	0.22	−0.5	−1.3	0.3	0.18	−0.4	−2.2	1.3	0.61
Attention problems	2.5	0.6	4.4	0.01	1.2	0.0	2.5	0.06	1.3	−1.0	3.5	0.26
Aggressive behaviour	−0.8	−2.9	1.3	0.42	−3.1	−4.4	−1.9	<0.001	2.3	−0.1	4.7	0.06
Rule-breaking behaviour	−2.2	−3.4	−1.1	<0.001	−3.7	−4.7	−2.6	<0.001	1.5	−0.1	3.0	0.06
Internalising problems	6.9	2.4	11.4	0.004	2.2	−0.6	5.0	0.11	4.7	−0.5	9.9	0.08
Externalising problems	−1.8	−4.5	0.9	0.18	−5.3	−7.3	−3.4	<0.001	3.6	0.3	6.8	0.03
Total problems	9.1	−1.6	19.9	0.09	−0.5	−6.9	5.9	0.87	9.7	−2.7	22.0	0.12

EP = extremely preterm, CI = confidence interval.

Raw scores are given for all scales. Higher scores indicate more problems.

Analysed performed with linear longitudinal regression models with group (EP-born vs. term-born), age (18 vs. 27 years) and the group–age interaction as explanatory variables.

[a] At 18 years 31 cases, and at 27 years 21 cases.

[b] At 18 years 29 term-born controls, and 27 years 26 term-born controls.

[c] Estimate of 27 years minus 18 years.

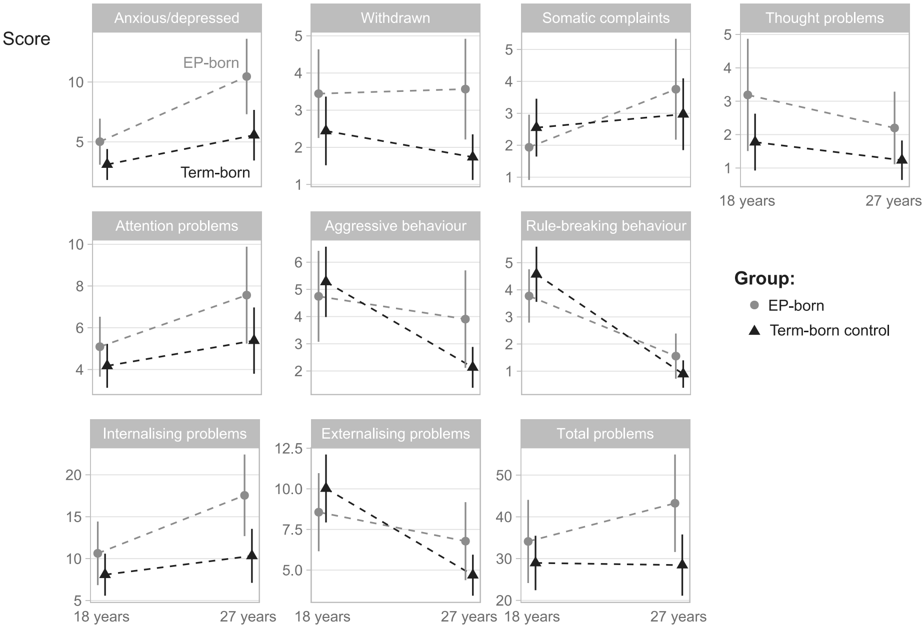

Fig. 2. Estimated change in mental health syndromes scales (YSR, ASR), with 95 % confidence internal, at 18 and 27 years for the EP-born and term-born controls. Increasing scores imply more mental health problem.

population [25]. This contrasts our previous study of a cohort born in the early 1980s [15], where EP-born had poorer HRQoL scores in almost all domains. This leads us to speculate if individuals born EP in the modern era of neonatal intensive care, after the introduction of surfactant (such as this present 1991–92 cohort), may fare better on HRQoL. Our data is difficult to interpret on this, as the 1980 and 1990 groups differed on disabilities like cerebral palsy, which will have an influence on HRQoL. Morbidity and disability data from this cohort are in line with similar cohorts of extremely preterm born infants [49].

4.1. Strengths and limitations

The major strengths of the study were the population-based design and the relatively high follow-up rate, and the fact that we have information about the non-participants. No subjects in this cohort had major impairments, therefore the results may not be representative to those with neurosensory impairments such as CP, severe hearing or visual deficits, or low IQ. Further, we used validated measurements for self-reported mental health and HRQoL.

The major limitation was the low number of participants, so the findings must therefore be cautiously interpreted, especially non-significant group differences. Attrition is a challenge in longitudinal studies, but the participation rate was comparable to other follow-up studies with similar study populations [50], and participants and non-participants were similar when compared by important background data. It has to be noted that our participants were born and raised in a country with universal access to health care for all, and therefore results may be seen most relevant to similar societies.

5. Conclusion

Mental health problems increased from 18 to 27 years age in EP-born adults and exceeded those of term-born controls, while HRQoL between groups was similar. The data suggest that extremely preterm birth should be considered a high-risk factor for poor mental health in adulthood, and support a proactive attitude to mitigate this during younger ages.

Funding

This study was financially supported by the Western Norway Regional Health Authority.

CrediT authorship contribution statement

MB: Conceptualised, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Validation. **BV:** Conceptualised, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Validation. **JD:** Formal analysis, Writing – original draft, Writing – review & editing, Validation. **MV:** Funding acquisition, Investigation, Supervision, Writing – original draft, Writing – review & editing, Validation. **TH:** Funding acquisition, Methodology, Writing – original draft, Writing – review & editing, Validation. **KOH:** Supervision, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Validation.

Acknowledgements

We thank the participants for their generosity in participating in our ongoing study for many years.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2022.105661.

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Table S1 Characteristics at 27 years' follow-up of the participants and nonparticipants subjects born extremely preterm.

	Participated (*n* = 24)	Not participated (*n* = 11)	participants vs. nonparticipants *P*-value
Female, *n* (%)	14 (64.6)	8 (36.4)	0.41
Gestational age, weeks, mean (SD)	26.7 (1.7)	26.9 (1.9)	0.72
Birthweight, mean (SD)	944 (224)	910 (159)	0.62
Days on ventilator	10.0 (13.43)	4.8 (6.1)	0.13

Pearson's chi-squared or Welch's *t*-test as appropriate.

Table S2 Characteristics at 27 years follow up, of the participants and nonparticipants term-born controls subjects.

	Participated (*n* = 26)	Not participated (*n* = 9)	participants vs. nonparticipants *P*-value
Female, *n (%)*	18 (81.8)	4 (18.2)	0.19
Birthweight, mean (SD)	3540 (270)	3633 (295)	0.42

Pearson’s chi-squared or Welch’s *t*-test as appropriate.

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Received: 18 October 2023 | Revised: 26 January 2024 | Accepted: 29 January 2024

DOI: 10.1111/apa.17146

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ORIGINAL ARTICLE

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

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Funding information
Helse Vest, Grant/Award Number: F-12510

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

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.

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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.

a 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.

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.

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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

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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,

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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.

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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.

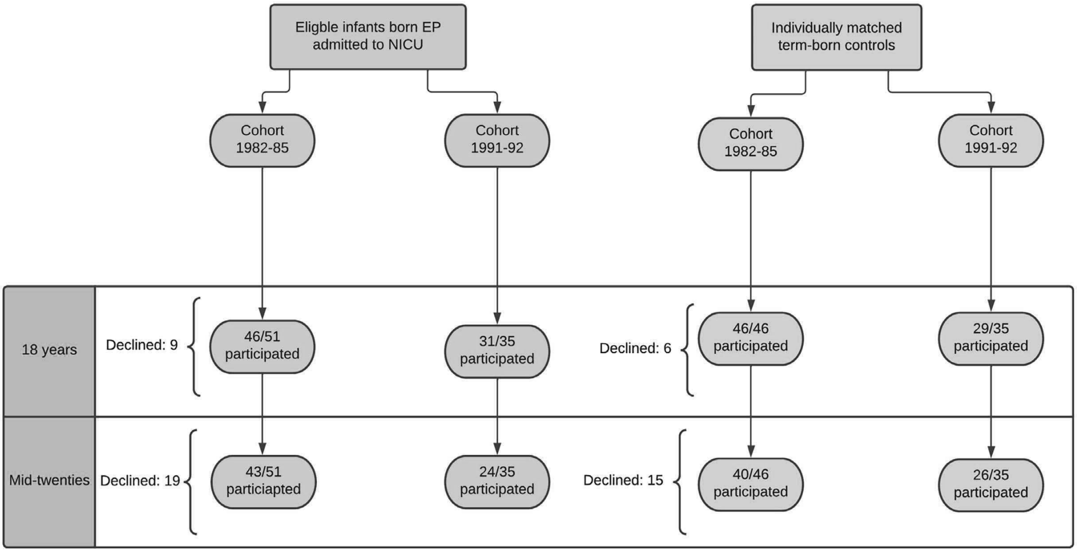

FIGURE 1 Flow chart of the extremely preterm (EP) born subjects and matched term-born controls from the two cohorts at the follow-up points.

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).

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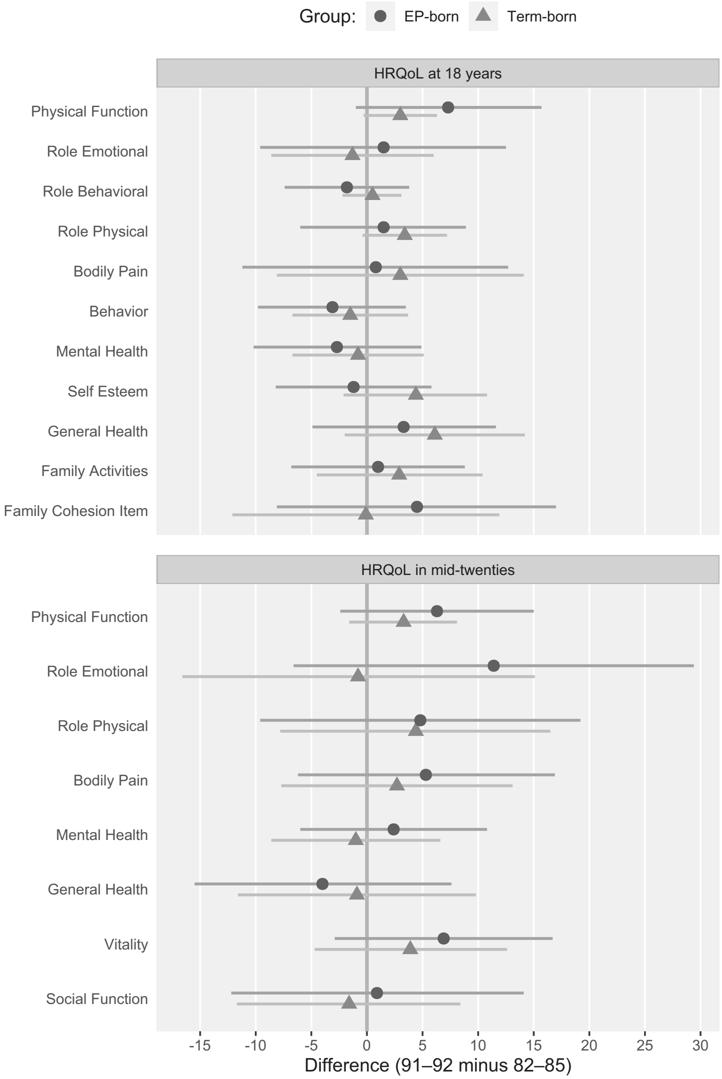

FIGURE 2 Mean differences and confidence intervals of self-reported HRQoL domains between the two cohorts of adults born extremely preterm (EP) and term-born controls. Analyses performed with regression analysis on multiply imputed data.

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

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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

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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.

ACKNOWLEDGEMENTS

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.

FUNDING INFORMATION

This study was funded by the Western Norway Regional Health Authority. The funder had no role in any aspect of the study or paper.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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How to cite this article: Benestad MR, Drageset J, Vollsæter M, Hufthammer KO, Halvorsen T, Vederhus BJ. Health-related quality of life in two birth cohorts of extremely preterm born adults. Acta Paediatr. 2024;00:1–10. https://doi.org/10.1111/apa.17146

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Table S1 Estimated predictive effect of birth cohort (91–92 vs. 82–85), postnatal steroids (yes vs. no), gender (female vs. male) and maternal education (higher vs. not higher) on HRQoL at 18 years of age in adults born EP. The reported estimates are coefficients estimates from a multiple regression analysis.

	91-92 cohort Estimate (CI; P)	**Steroids Estimate (CI; P)**	**Female Estimate (CI; P)**	**Mother's higher education Estimate (CI; P)**
CHQ-CF87[a]				
Physical Function	6.8 (−3.3; 16.9; P = 0.18)	−2.1 (−15.8; 11.7; P = 0.77)	2.2 (−7.5; 11.9; P = 0.66)	−3.1 (−14.7; 8.6; P = 0.60)
Role Emotional	9.3 (−1.9; 20.6; P = 0.10)	−14.5 (−30.0; 0.9; P = 0.06)	**−18.9 (−29.4; −8.3; P < 0.001)**	**12.9 (−0.2; 26.0; P = 0.05)**
Role Behavioural	0.0 (−5.5; 5.4; P = 0.99)	−6.7 (−14.1; 0.7; P = 0.07)	−0.7 (−5.9; 4.5; P = 0.78)	3.6 (−2.4; 9.7; P = 0.24)
Role Physical	7.0 (−0.7; 14.7; P = 0.07)	**−16.5 (−26.9; −6.1; P = 0.002)**	**−7.7 (−14.9; −0.4; P = 0.04)**	**9.7 (1.0; 18.4; P = 0.03)**
Bodily Pain	6.9 (−5.8; 19.5; P = 0.28)	−13.9 (−31.1; 3.4; P = 0.11)	**−19.0 (−31.1; −7.0; P = 0.002)**	−0.2 (−14.6; 14.2; P = 0.98)
Behaviour	−0.6 (−7.4; 6.2; P = 0.85)	−7.2 (−16.3; 1.9; P = 0.12)	−5.8 (−12.3; 0.6; P = 0.08)	0.8 (−6.7; 8.3; P = 0.83)
Mental Health	1.9 (−5.4; 9.3; P = 0.60)	**−9.7 (−19.6; 0.2; P = 0.05)**	**−14.1 (−21.1; −7.2; P < 0.001)**	1.2 (−7.0; 9.4; P = 0.78)
Self Esteem	2.9 (−4.0; 9.9; P = 0.40)	**−10.6 (−19.9; −1.3; P = 0.03)**	**−12.3 (−18.9; −5.7; P < 0.001)**	−0.6 (−8.4; 7.2; P = 0.88)
General Health	6.5 (−2.3; 15.3; P = 0.15)	−9.1 (−21.0; 2.8; P = 0.13)	−6.9 (−15.2; 1.5; P = 0.11)	2.0 (−7.9; 11.9; P = 0.69)
Family Activities	2.7 (−5.6; 11.1; P = 0.51)	−6.9 (−18.6; 4.7; P = 0.24)	−2.7 (−10.5; 5.2; P = 0.50)	0.7 (−8.6; 10.1; P = 0.88)
Family Cohesion Item	3.9 (−9.7; 17.6; P = 0.57)	5.0 (−13.5; 23.4; P = 0.59)	−4.0 (−16.8; 8.8; P = 0.53)	−3.6 (−19.4; 12.1; P = 0.65)

The bolded values are statistically significant (p<0.05). Analyses performed with linear regression 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 S2 Estimated predictive effect of birth cohort (91–92 vs. 82–85), postnatal steroids (yes vs. no), gender (female vs. male) and maternal education (higher vs. not higher) on HRQoL in their mid-twenties in adults born EP. The reported estimates are coefficients estimates from a multiple regression analysis.

	91-92 cohort **Estimate (CI; P)**	**Steroids** **Estimate (CI; P)**	**Female** **Estimate (CI; P)**	**Mother's higher education** **Estimate (CI; P)**
SF-36[a]				
Physical Function	8.4 (−2.1; 18.9; P = 0.11)	−3.5 (−17.7; 10.6; P = 0.62)	−4.7 (−14.6; 5.2; P = 0.35)	4.3 (−7.1; 15.7; P = 0.45)
Role Physical	10.2 (−5.5; 26.0; P = 0.20)	−14.8 (−36.6; 6.9; P = 0.18)	−7.5 (−22.0; 6.9; P = 0.30)	10.5 (−7.4; 28.3; P = 0.25)
Bodily Pain	11.1 (−1.6; 23.9; P = 0.08)	−11.0 (−27.5; 5.6; P = 0.19)	**−13.1 (−24.5; −1.6; P = 0.03)**	10.0 (−3.6; 23.6; P = 0.15)
General Health	1.2 (−10.8; 13.2; P = 0.84)	**−17.0 (−33.4; −0.6; P = 0.04)**	−11.0 (−22.5; 0.5; P = 0.06)	0.4 (−13.0; 13.9; P = 0.95)
Vitality	10.6 (0.1; 21.1; P = 0.05)	−11.7 (−26.0; 2.6; P = 0.11)	−6.9 (−17.0; 3.1; P = 0.17)	2.2 (−9.2; 13.5; P = 0.70)
Social Function	7.1 (−7.0; 21.1; P = 0.32)	**−21.9 (−40.6; −3.1; P = 0.02)**	−8.2 (−21.0; 4.6; P = 0.21)	6.1 (−9.2; 21.3; P = 0.43)
Role Emotional	13.0 (−7.0; 32.9; P = 0.20)	−8.9 (−35.2; 17.4; P = 0.50)	2.8 (−16.1; 21.7; P = 0.77)	4.8 (−17.2; 26.8; P = 0.66)
Mental Health	4.1 (−4.8; 13.0; P = 0.36)	−7.3 (−19.2; 4.5; P = 0.22)	−2.4 (−10.9; 6.1; P = 0.57)	−0.2 (−10.0; 9.5; P = 0.96)

The bolded values are statistically significant ($p<0.05$). Analyses performed with linear regression 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.

Table S3 Missing values of the questionnaires from the participants of both cohorts.

Cohort	**82–85**	**82–85**	**91–92**	**91–92**
Case/Control	Case	Control	Case	Control
Child Health Questionnaire Child Form-87 (CHQ-CF87)				
Physical Function	3	0	4	6
Role Emotional	3	0	4	6
Role Behavioural	3	0	4	6
Role Physical	3	0	4	6
Bodily Pain	3	0	4	6
Behaviour	3	0	4	6
Mental Health	3	0	4	6
Self Esteem	3	0	4	6
General Health	3	0	4	6
Family Activities	4	0	4	6
Family Cohesion Item	3	0	4	6
Short Form Health Survey (SF-36)				
Physical Function	6	6	11	10
Role Physical	6	6	11	10
Bodily Pain	6	6	11	10
General Health	6	6	11	10
Vitality	6	6	12	10
Social Function	6	6	11	10
Role Emotional	6	6	11	10
Mental Health	6	6	12	10

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

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ISBN: 9788230860144 (print)
9788230850640 (PDF)