

Health-Related Quality of Life, emotional and behavioural difficulties and perception of pain after extreme preterm birth – a population-based longitudinal cohort study

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Scientific environment

This dissertation originated from the Department of Global Public Health and Primary Care, the Faculty of Medicine and Dentistry at the University of Bergen, Norway. My main supervisor was Professor Gerd Karin Natvig, Head of the Research Group on Quality of Life. The main research environment was the Department of Paediatrics at Haukeland University Hospital, part of the Department of Clinical Science at the University of Bergen. My co-supervisors were Professor Trond Markestad, Coordinator of the Research Group for Paediatric Follow-up Studies; Professor Thomas Halvorsen, Research Group for Paediatric Follow-up Studies; and Professor Marit Graue, the Centre for Evidence-based Practice at Bergen University College. Professors Markestad and Halvorsen are paediatricians. Professor Geir Egil Eide, a biostatistician from the Centre for Clinical Research, Haukeland University Hospital, supervised the statistical analyses performed for the studies described in this dissertation.

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Ever since I first started working in the Neonatal Intensive Care Unit (NICU) in Ålesund in 1985, and then at Haukeland University Hospital in Bergen in 1990, my work has been dedicated to the field of neonatal care. From the beginning, I have been especially attracted to tiny, vulnerable preterm-born neonates. They have never stopped engaging me, and they continue to challenge my knowledge on how best to care for them and their families in order to provide a good start in life. Becoming a trained NIDCAP observer expanded my understanding of the behaviour of neonates and the importance of including parents in the care of their children from the very moment of admission to the NICU.

In 2008, I was invited to join the Research Group for Paediatric Follow-up Studies at the Department of Paediatrics at Haukeland University Hospital. Professor Thomas Halvorsen was about to start the second follow-up of two preterm born cohorts of adolescents and young adults. This event represents the start of the work reported in this dissertation, which has been my part-time job for six years. It has been challenging work and at times also frustrating, but I feel privileged to have had the opportunity to do this work and to realize a dream. I am truly indebted to all my supervisors for their inspiring and optimistic support and valuable mentoring throughout the process leading to this dissertation. They all deserve special mention.

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Preface

“A preterm’s story”

I was born in the early eighties at gestational week 27 and weighed about 630 grams. Now, many years later I have several questions to be answered. Do we know anything about the prospects of staying employed? Is there any knowledge that shows how prematurity affects the ability to work?

I have lived a ‘normal’ life, I have completed a college degree, and my prematurity was not a focus during my upbringing. Everything turned out so well considering the circumstances: I survived! Nevertheless, I feel different.

I had major sleep issues as a child. I was bullied in school. I was/am sensitive to changes and various moods. And I am influenced by all of this. I was/am cautious and insecure, in general. I was/am a slow learner. And I am not close to my mother. At the moment, I am on sick leave from my job, a part-time position, due to depression and anxiety, which I also had when I had another kind of employment. I have always found it a challenge to master the workplace — the pace is too quick and I am easily stressed. Lately, I have wondered if there is a link to being born prematurely. I find that this is a difficult topic to bring up with the doctor I am consulting regarding sick leave/employment. Is there anything or anyone that can enlighten and support me? Any literature or research or advice from an expert?



“Thank you for sharing”

Abstract

Background: Rates of preterm birth vary widely among countries, proportions ranging from around 6% in Scandinavia, 12% in the United States to 18% in some African countries. Due to progress in perinatal medicine, there has been a substantial increase in survival after extreme preterm birth (gestational age < 28 weeks) over the past decades, accounting for about 0.4% of births in Norway. Extreme preterm birth poses tremendous challenges to neonates and their families from the very beginning. Preterm birth may have lifelong consequences for neurodevelopmental functioning in terms of motor, cognitive and psychosocial skills, and may contribute to development of various chronic diseases. When investigating these possible effects, researchers typically employ traditional measures of morbidity (i.e., objective measures of function). Self-reported opinions of health and well-being and how they vary throughout life have received less research attention.

Aims: The overall aim of this dissertation work was to investigate how extreme preterm birth affects health and well-being throughout childhood and early adulthood. We compared the developmental trajectories of health-related quality of life (HRQoL), emotional and behavioural patterns, and perception of and responses to pain of subjects born preterm to those of matched control subjects born at term.

Methods: This was a population-based longitudinal matched controlled cohort study of subjects born at a gestational age of ≤ 28 weeks or with a birth weight of ≤ 1000 grams and of gender- and age-matched term-born (TB) controls. The participants were born within a defined region of Western Norway during two periods: 1982-1985 (46 preterm babies) and 1991-1992 (35 preterm babies). The Child Health Questionnaire and Child Behaviour Checklist were applied when the children reached the age of 10 years and in late adolescence (18 years), supplemented with the Youth Self-Report, General Self-Efficacy, and health complaints questionnaire at 18 years; and the Short Form Health Survey-36 and health complaints questionnaire in young adulthood (24 years). At 18 years of age, their pain tolerance and pain perception were measured using a standardized Cold Pressor Task (hand in ice water).

Results: The longitudinal response rates were high at 89% and 84%, respectively, for the preterm-born subjects, and 83% and 87%, respectively, for the control term-born subjects.

The parents of the 1991-1992 preterm-born cohort reported that their children had inferior HRQoL in nearly all domains at 10 years of age, including the family and parent domains, and more emotional and behavioural difficulties compared to age-matched TB children. The differences were especially evident for preterm-born boys, but minor for preterm-born girls. When these children reached adolescence (age 18), the parents reported improved HRQoL and behaviour for the preterm-born boys, achieving scores approaching those of the TB boys. The girls, however, remained relatively unchanged. Early emotional and behavioural difficulties predicted less improvement in HRQoL for all participants. The preterm-born adolescents reported their HRQoL, behaviour, and pain perception to be relatively similar to those of their TB peers, but their actual pain tolerance was inferior, especially the preterm-born boys. General Self-Efficacy was associated with better HRQoL, behaviour, and pain tolerance for all participants.

Also the 1982-1985 preterm-born cohort reported HRQoL and health complaints to be relatively similar to those of their TB peers when in *their* adolescence (age 17), except for inferior physical functioning for the impaired preterm-born subjects. At adulthood (age 24), the healthy preterm-born subjects reported poorer psychosocial functioning and more psychological health complaints compared to their TB peers.

Conclusion: These findings demonstrate that extremely preterm-born subjects have inferior HRQoL and more behaviour problems in childhood, as reported by their parents. These characteristics improved through adolescence, especially for the boys. Severe behaviour problems in childhood predicted less improved HRQoL through puberty. At 18 years, extreme preterm-born subjects reported relatively similar HRQoL and behaviour as term-born controls, whereas in adulthood a tendency for inferior psychosocial HRQoL became apparent, particularly in those *without* disabilities. We also found lower pain tolerance but similar perception of pain at 18

years. Our findings underscore the importance of obtaining subjective knowledge of health and well-being, both from the perspective of parents and the preterm-born subjects. Moreover, it is important to observe changes through critical developmental phases in life, such as puberty, and to further explore the observed effects of gender that may be of importance. Finally, health professionals treating subjects who were born prematurely should be aware of a potential for unexpected pain responses in these individuals.

List of publications

- Vederhus BJ, Eide GE, Graue M, Natvig GK, Markestad T, Halvorsen T. Health-related quality of life after extremely preterm birth: a matched controlled cohort study. *Health and Quality of Life Outcomes* 2010; 8:53
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- Vederhus BJ, Eide GE, Natvig GK, Markestad T, Graue M, Halvorsen T. Health-related quality of life and emotional and behavioral difficulties after extreme preterm birth: developmental trajectories. *PeerJ* 3:e738 <http://dx.doi.org/10.7717/peerj.738>
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Abbreviations

ASEBA	Achenbach System of Empirically Based Assessment
ADHD	Attention deficit hyperactivity disorder
BPD	Bronchopulmonary dysplasia
BW	Birth weight
CBCL	Child Behaviour Checklist
CHQ	Child Health Questionnaire
CI	Confidence interval
CPT	Cold Pressor Task
CUS	Cerebral ultrasonography
FEV ₁	Forced expiratory volume in the first second
ELGA	Extremely low gestational age
ELBW	Extremely low birth weight
EP	Extremely preterm: < 1000 grams or < 28 weeks
GA	Gestational age
GSE	General Self-Efficacy
HBSC-SCL	Health Behaviour in School-aged Children – Symptom Checklist
HRQoL	Health-Related Quality of Life
IVH	Intraventricular haemorrhage
LMP	Last menstrual period
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NIDCAP	Newborn Individualized Developmental Care and Assessment Programme
NRS	Numeric Rating Scale
PVL	Periventricular leucomalacia
ROP	Retinopathy of prematurity
SGA	Small for gestational age
SES	Socioeconomic status
SF-36	Short Form 36 Health Survey

SD	Standard deviation
TB	Term born
VLBW	Very low birth weight
WHO	World Health Organization
YSR	Youth Self-Report

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1. Background

A child who is born extremely preterm (EP) is faced with a challenging medical condition treated in an artificial and developmentally unexpected environment, is repeatedly exposed to stressful and often painful events for several months, and is mostly separated from its parents. All of these factors may have harmful effects on the development of the child¹. Survival rates after extreme preterm birth have increased substantially over the past 2-3 decades with the advent of modern neonatal intensive care and advances in maternal-foetal medicine^{2,3}. For neonates admitted to a neonatal intensive care unit (NICU), approximately 40% survived at 23 weeks and 90% at 27 weeks in a Norwegian national cohort born in 1999-2000⁴. Important prerequisites for this development were a shift in medical treatment and care, including implementation of antenatal and postnatal corticosteroid in the 1980s and surfactant treatment in the early 1990s, and application of new technical equipment on basically all levels, adapted to the care of small neonates, thereby facilitating better ventilator strategies and overall care and surveillance^{5,6}. Throughout the last decades there have been continuous improvements in our understanding of the needs of preterm-born individuals, medical knowledge, technological support, and nursing care. Improvements in nursing care, for example, have introduced a higher level of parental involvement and participation in the care of their neonate. However, irrespective of the era of birth, treatment and care are demanding for parents and children who are hospitalized for months. For infants born EP in Norway in 1999-2000, the median hospital stay was 84 days⁴.

Being born preterm, and especially EP, is associated with increased risk of cognitive and social limitations, neurosensory deficiencies, emotional and behavioural problems, psychiatric disorders, pulmonary problems, cardiovascular and metabolic diseases, and even early death⁷⁻⁹. There is an increasing risk of disabilities with decreasing gestational age^{8,10-12}. Thus, increased survival of immature children might conceivably contribute to more preterm-born children with disabilities growing up. However, increased survival rates of the most immature babies during the period 1995-2006 did *not* lead to an increased rate of disabilities at three years of age¹³.

Furthermore, a *reduction* in severe morbidity in neonates born before 28 weeks pregnancy has recently been published ¹⁴. Despite these optimistic signals, survival of more vulnerable children nevertheless represent a public health challenge ^{15,16}. We therefore need increased knowledge on outcomes for the preterm-born population and on the complex range of potential influence from non-medical and medical factors. While the early literature on the outcomes of preterm birth focused mainly on traditional measures of morbidity with an emphasis on major impairments, contemporary literature shows that more research attention has been focused on less severe dysfunction that is more prevalent and that may have negative consequences for health and social function ¹⁷. This includes the subjective experiences of the preterm-born child and the family to create an overall understanding of the long-term effect on health and well-being after preterm birth. There is sparse knowledge on these latter issues.

Hence, the focus of the present thesis work was to examine long-term development of health in preterm-born subjects over time. We quantified this by measuring health-related quality of life (HRQoL), health complaints, emotional/behavioural difficulties, and the perception of pain after extreme preterm birth, as reported by parents and the subjects themselves in two geographically defined populations born EP in the two periods 1982-1985 and 1991-1992. This was one part of a comprehensive follow-up study, entitled *Lung function, working capacity, and quality of life after extreme preterm birth*.

1.1 Definitions

Two measures have been used in the research literature to classify preterm-born neonates: (1) gestational age (GA: postmenstrual age at delivery), and (2) birth weight (BW). The details of these two measures are summarized in Table 1 ^{18,19}.

Table 1. Categories of prematurity and low birth weight

	Birth weight (grams)	Gestational age (weeks)
Post-term birth		≥ 42
Term birth		37 - 41

Preterm (premature) birth	< 37
Late preterm birth	34 - 36
Moderate-to-late preterm birth	32-33
Very preterm birth	28-31
Extremely preterm birth	< 28
Low birth weight	< 2500
Very low birth weight	< 1500
Extremely low birth weight	< 1000

1.2 Epidemiology

A report from 2010 estimated that 14.9 million children (11.1%) were born preterm, (born before 37 weeks of pregnancy), with a range from around 5% in Europe to 18% in some African countries¹⁸. Although the highest rates were concentrated to sub-Saharan Africa and South Asia, even in the United States, the rate can reach as high as approximately 12%¹⁸. Approximately 6% of all births in Norway are preterm, totalling approximately 3500 babies per year^{18,20}. Norway, together with the other Scandinavian countries, has a relatively low incidence of preterm birth.

Complications related to preterm birth are the second largest cause of child mortality under the age of five, and for surviving babies, these may have lifelong adverse consequences on development and health¹⁸.

1.3 Aetiology of preterm birth

Generally, preterm birth is categorized as either spontaneous preterm birth or provider-initiated preterm birth^{18,21}. In the latter, labour is induced due to maternal or foetal factors, totalling approximately 30%, while spontaneous preterm birth, including spontaneous labour and preterm premature rupture of the membranes, is considered to be a syndrome with multifactorial causes^{18,21}. In many cases, the causes are unknown, but many factors such as infection or inflammation, cervical uterine conditions, multiple gestations, individual and family history of preterm birth,

nutritional state, young as well as advanced maternal age are associated with spontaneous preterm birth^{18,21}.

1.4 Neonatal mortality and morbidity

The lower GA limits for possible survival and for initiating active treatment is a recurring bioethical discussion in the field of neonatology. A recently published paper reported that the general international consensus is to offer comfort care at 22 weeks GA and full resuscitation at 24 weeks²². In Norway the GA limit for offering resuscitation has been between 23 to 25 weeks completed weeks²³. Figures from Sweden showed 70% one-year survival for live-born, EP infants with GA below 27 weeks in 2004-2007 accompanied with neonatal morbidity in about half of the survivors²⁴. In the Norwegian Extreme Prematurity Study for infants born in 1999-2000, approximately 80% of infants admitted to the NICU were discharged alive from hospital⁴. Similar figures have been reported for infants born in the United States in 2003-2007²⁵. These figures contrast sharply with those from low-income countries, which show that infants born at 32 weeks GA or less than 2000 grams have little chance of survival²⁶.

In the aforementioned studies from high-income countries, the survival rate increased with increasing GA, and the risk of morbidity increased with decreasing GA. The most common complication related to prematurity are pulmonary insufficiency with respiratory distress syndrome and bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), periventricular and intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), and infections^{4,24,25}.

Respiratory distress syndrome is due to the lungs being immature, specifically lacking alveolar surfactant and structural maturity. For preterm neonates, this manifests as respiratory insufficiency, requiring respiratory support with continuous positive airway pressure or mechanical ventilation and oxygen. The degree of distress tends to increase with decreasing GA, with an incidence of 92% at 24-25 weeks GA to 76% at

28-29 weeks GA and around 50% at 30-31 weeks GA²⁷. BPD is defined as being dependent on supplemental oxygen for ≥ 28 days (mild) or at 36 weeks GA (moderate/severe)²⁸ and may be followed by airway obstruction into adulthood, as reported in our two cohorts²⁹.

ROP is a disease related to vascular abnormalities of the retina and may lead to impaired vision and, in the worst case, to blindness. The incidence of blindness due to ROP depends on the level of the requirements for neonatal intensive care, particularly supplemental oxygen. Screening and treatment programmes implemented in more highly developed countries have resulted in great improvements compared to in less developed countries, where these programs have not been implemented or may be less applicable^{30,31}. Norwegian figures of ROP demonstrate decreasing rates with increasing GA, with around 60% at 24 weeks GA and 15% at $> 27 < 28$ weeks GA⁴.

The brain of the preterm neonate is fragile and vulnerable to injury, because major structural and organizational development meant to take place in a protected environment inside the womb must occur within the frames of a neonatal intensive care unit (NICU)³². There is a marked risk of ischaemia, IVH, and PVL, which can be identified with cerebral ultrasonography (CUS) or magnetic resonance imaging (MRI)³². The Norwegian Extreme Prematurity Study reported that 38% of their preterm-born neonates exhibited CUS pathology⁴. Severe brain injury of this kind is a risk factor for neurodevelopmental impairment^{32,33}.

In addition, the gastrointestinal tract of these neonates is immature and is susceptible to ischaemia and infection, leading to NEC at an incidence of approximately 6% and 11% in EP-born neonates in respectively Sweden and the United States^{25,34}.

Surgically treated NEC is associated with poor neurodevelopmental outcome³⁵.

Neonatal sepsis is a major risk factor for death and neonatal morbidity, and the Norwegian Extreme Prematurity Study reported an incidence of about 6% for early onset sepsis (within first week) and about 20% for late onset sepsis ($>$ six days of age)^{36,37}.

1.5 Follow-up studies and risk factors

Preterm birth is a risk factor for a series of functional deficits during the child's lifespan. Individual biological and medical factors interact with social, familial, personal, cultural, and environmental factors in complex ways to influence the development of the infant³⁸.

A recent review of risk factors related to long-term neurodevelopmental outcome concluded that early GA and low BW were strong predictors for adverse outcome³⁹. Brain injury, male gender, NICU care such as mechanical ventilation and postnatal corticosteroid treatment, and socioeconomic factors also affected outcomes³⁹.

Depending on the developmental stage the child has reached, different measures can be used for assessing a preterm-born child, and different predictors of outcomes may be relevant⁴⁰.

The increased risk of severe neurosensory-developmental disabilities in preterm-born children was inversely related to decreasing GA, and many of these disabilities were diagnosed before the age of two^{41,42}. Deficits are usually categorized into severe or mild-to-moderate deficits, with the severe class including cerebral palsy, mental retardation (< 70 intelligence quotient [IQ] points), and severe visual or hearing impairment^{41,43}. In the Norwegian Extreme Prematurity Study (GA < 28 weeks or BW < 1000 grams), the incidence of severe impairments at two years of age in the 373 surviving children was 7% for cerebral palsy, 2% for blindness, 1% for deafness⁴⁴, relatively similar to a Swedish study (GA < 27 weeks)⁴⁵, while rates of 14% for cerebral palsy, 1% for blindness and 7% for deafness were reported in a US population with BW < 1000 grams born during 1990-1998³. In a Swedish study of infants born less than 26 weeks GA in 1991-1992, major disabilities assessed at 11 years of age were associated with severe ROP and brain injury³³. In the Norwegian study, higher cognitive and motor abilities in children without severe disabilities were associated with higher educational attainment of the mothers, female gender, and lack of severe ROP⁴².

Impaired cognitive skills and lower school performance, together with behavioural problems are frequently reported in school-aged preterm-born children, and these characteristics represent major challenges for these children, particularly for those without major neurosensory-developmental disabilities⁴⁶. More emotional and behavioural problems occur in 5-year-olds in the Norwegian national cohort of children born EP, also in children without neurodevelopmental disabilities⁴⁷. This has been found in less preterm-born children as well⁴⁸. The rates of special educational assistance for EP-born child populations in the 1980s ranged from 39% to 62% in an international study of four countries in Europe and in North America⁴⁹. Executive dysfunction with lack of purposeful and goal-directed behaviour has also been reported in preterm-born children, in school age⁵⁰⁻⁵², in late adolescence⁵³, and into adulthood⁵⁴. This was predicted by lower BW, small for gestational age (SGA), and longer periods of oxygen requirement⁵³. When comparing results across four decades of cognitive research, better cognitive skills are more likely to be present in populations born preterm after 2000 compared to those born in earlier eras of prenatal and neonatal intensive care³⁸.

In a review article of sequelae of preterm-born children followed into adulthood, higher rates of mental and emotional delays were reported, as well as limitations of daily living and self-care capabilities compared to TB peers⁵⁵. Still, adult functioning was better than expected based on the many difficulties that were reported in childhood and adolescence⁵⁶. Concerning behavioural problems after preterm birth, a 3-8 fold increased risk has been observed for these individuals in adolescence when compared to TB peers⁵⁷. These behavioural problems were characterized by the presence of inattention, anxiety, and social problems^{57,58}. Furthermore, there is an increased risk of psychiatric disorders compared to the general population, more specifically diagnoses of attention deficit hyperactivity disorder (ADHD), autism spectrum disorders, and emotional disorders, especially anxiety⁵⁸. In a Norwegian register-based study of adults who were born preterm in 1967-1983, being preterm was associated with an increased risk of receiving social security benefits, being less likely to establish a family, and less likely to achieve higher academic attainment compared to those born at term¹². In general, preterm-

born subjects seem to have lower risk-taking behaviour compared to controls, including possessing lower rates of smoking, alcohol, and drug use^{8,56}.

2. Theoretical framework

2.1 Health

The word health has its origin in the old Germanic word ‘*hailson*’ and the old Nordic ‘*heill*’, which means whole, happiness, or lucky⁵⁹. More recently, its connotation has shifted to a more specific concept. In 1946 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*’⁶⁰. This multidimensional definition is much broader than simply a medical view, which restricted the notion of health to the absence of disease based on statistical normality⁶¹. The WHO definition by contrast is a holistic definition, including other aspects such as well-being⁶². Thus, health is regarded as a primary concept moving beyond disease⁶². While the medical model claims to be value-free, the holistic model embraces subjectivity. Health can be expressed in an individual’s abilities or strength in the presence of disease⁶³, and such personal characteristics may be evaluated in relation to health. As such, the definition may be seen as neither exclusive nor exhaustive, indicating that one can be healthy when disease is present or unhealthy when disease is absent. Hence there may be different levels of health. This view is not without controversy, however, and is disputed⁶². When empirically testing the dimensions of health and symptoms of disease, they appear to be related constructs that affect each other^{64,65}. WHO defines health in positive terms by integrating physical and psychosocial well-being. This definition, however, is criticized for lacking theoretical clarification and for being too comprehensive and idealistic, and of little value⁶³. Still, major programmes in health research that use self-reports have at their core this definition and understanding of health⁶⁶.

2.2 Health-Related Quality of Life (HRQoL)

HRQoL is constructed from health and quality of life. These constructs are sometimes used synonymously, which can create confusion about the meaning. Quality of life is

generally understood as satisfaction with life and happiness, and is a broader concept than that encompassed by HRQoL⁶⁷. Within biomedicine, morbidity and mortality were the traditional outcome measures for evaluating health care, but with advances in medical treatment and technology and increased life expectancies, assessment of quality of life became important as well^{66,68}. Starting in the 1970s, there was an increasing interest in quality of life research, resulting in an accumulating number of publications in psychology, biomedicine, sociology, and nursing^{68,69}. While quality of life was regarded as an all-embracing construct, it was narrowed by the introduction of HRQoL^{67,69,70}. Hence the impact from health, disease, and medical treatment on quality of life became the focus. Thereby, aspects that did not directly concern health, such as political, cultural, and sociological aspects of life, were excluded⁶⁹. However, environmental and individual factors have been included in models of HRQoL^{69,71}.

With the beginning of WHO's definition of health, HRQoL was operationalized into domains of physical, psychological and social functioning, and well-being⁶⁶. Functioning emphasized the consequences of health on performing activities of daily living and social life, while the positive well-being aspect dealt with how health might affect wellness⁷². Both cognitive and emotional processes are involved in the subjective experience of an individual⁶⁶. Accordingly, individuals with similar health status may perceive their HRQoL very differently through their evaluation of their capabilities⁷³. Some claim that health status is a superior construct to HRQoL. However, inherent in the discussion is the mixture of quality of life and health as representing the same construct while also being distinct in some respects, as highlighted by Moons^{66,68}.

2.2.1 HRQoL in children

When children are assessing their HRQoL, some theoretical and methodological challenges arise^{74,75}. Developmental processes affect children's social, emotional, cognitive, and biological competencies, factors that have to be integrated in both the conceptualization and operationalization of HRQoL^{74,75}. The child's understanding

of health, well-being, and disease, and what influences these issues changes during their development^{74,75}. The fundamental developmental changes of physical, psychological, and emotional character that occur during puberty may affect health⁷⁶. In general, girls and boys report similar HRQoL in childhood; however, during adolescence there is a decline, especially in girls^{65,77-79}.

Self-reflection and ability to think abstractly is considered to be necessary when judging one's HRQoL, and from eight years of age, children are considered to be capable of self-reporting^{74,75,79}. Parents may well rate their child's HRQoL, but the use of reports completed by both child and parents may be preferable^{70,75,80}.

Researchers within the paediatric field have acknowledged that the emotional and social needs of the family must be included in the concept of HRQoL in children^{70,81}.

2.3 Emotional and behavioural difficulties

Throughout childhood, many children, as well as adolescents, may experience some kind of emotional and behavioural difficulties that resolve as the child grows older and achieves better self-regulation. Behaviour is learned and modified and regulated by experiences in a continuous interaction of intrapersonal factors (biological, cognitive, affective) and environmental factors⁸². During development the child has different developmental tasks to accomplish that are affected by their sociocultural rearing environment, especially within the family⁸³. When developmental milestones such as social-emotional competence are not successfully accomplished, there is an increased risk for behaviour problems as well as psychopathology⁸³.

Emotional and behavioural difficulties may affect the well-being and mental health of the child. These difficulties may be symptoms of a mental health problem, but not a mental disorder^{84,85}. It is reflected in the child's behaviour and functioning, which can be assessed in different ways and categorized according to the nature of his or her problems^{83,84}. As for HRQoL during puberty, there seems to be both age- and gender-related changes, with generally fewer problems and better self-regulation with increasing age, however, somewhat dependent on the nature of problems⁸⁶. This tendency is reflected in studies of Norwegian children^{87,88}.

There are many potential factors that may contribute to behavioural problems in EP-born children⁸⁹. It is known that parents and the family environment have a substantial impact on the development of the child, and especially children at risk such as the EP born^{90,91}. Family and parents of preterm-born children are faced with specific challenges from birth of the child onward, specifically the extensive pressure of having a critically ill child, the separation from the child, and the neonate's immature expression and limited responsivity. Increased parental stress may disrupt a parent's sensitivity and awareness towards the child and cause dysfunctional parenting, all having a negative impact on the child's development⁹¹⁻⁹⁴. Inherent in this is the idea that the child's temperament interacts with parenting during development of self-regulation, and temperamental children may be more susceptible to certain experiences and interactions⁹⁵. Compared to a TB child, a preterm-born child may be more demanding, have vague expressions, poor self-regulation, and lower capacity to interact socially⁹⁵. With the history of prematurity, these children may have more difficult temperament and poor self-regulation and depend more on their parents to develop self-regulatory control⁹⁵.

2.4 Pain

Pain is well recognized as '*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*'^{96,97}. This definition underscores the subjective element of the experience and reveals that pain is multidimensional in character and encompasses much more than just a physical tissue-damaging event, such as a noxious stimulus. Melzack and Wall's (1965) gate-control theory demonstrated that the pain experience and pain response is a consequence of interacting mechanisms, in which the spinal cord acts like a gate that either blocks pain signals to the brain or allows them to persist⁹⁸. Other pain-modulating mechanisms have later been identified⁹⁸. These modulating mechanisms can either enhance or inhibit pain and are influenced by factors of both physical and psychological character⁹⁸, as reflected in the biopsychosocial model of pain⁹⁹. From this perspective, pain is a dynamic experience resulting from biological,

psychological, and social conditions related to the past and the present. The biological factors include disease-related conditions and noxious events, as well as age and gender. The psychological factors include a person's cognition and emotions, which influence the understanding of physiological cues and subsequent behaviour; with also sociocultural factors influencing both understanding and behaviour^{99,100}. Pain and different types of emotions interact in several ways and may further interact with cognitive appraisal of the pain situation, which may be shaped by the perception of control and efficacy to act in a desirable way⁹⁹. The biopsychosocial approach has been essential when dealing with chronic pain^{99,100}. The significance of the different components of this approach have been addressed in research, including cognitive behavioural interventions^{99,101,102}.

Pain is categorized according to the time course over which it is experienced, and can broadly be divided into either acute or chronic pain. Acute pain is often intense in character, shorter in duration, and is a result of a tissue-damaging event of different kinds and severity¹⁰³. Chronic pain may or may not be intense, is considered to last for minimum of three months, and may be persistent or recurrent⁹⁹. A feature that differentiates it from acute pain, is that it is not simply a symptom of injury or disease but a result of multiple interacting causes¹⁰³.

When it comes to children born preterm — who during rapid brain development are exposed to multiple and repetitive pain events caused by their medical condition and treatment — researchers and health professionals have long feared that these early pain experiences might have deleterious consequences in the long term¹⁰⁴⁻¹⁰⁸. Due to an immature central nervous system, several mechanisms contribute to ongoing discomfort during the neonatal period, a situation resembling more a chronic condition¹⁰⁹. Stress and pain are closely related, and the critical factor(s) distinguishing the two clinically and which of them is impacting development, are difficult to disentangle^{109,110}. These early life events are considered to be important for neurodevelopment (especially the developing brain), stress systems, and development of pain sensitivity^{108,109}. A recent review highlights several studies showing altered brain development associated with greater exposure to pain and

stressful events¹⁰⁸. Furthermore, neonatal pain exposure has been associated with behavioural changes and an altered basal and diurnal level and response of the stress hormone cortisol^{108,109,111-114}.

2.5 General Self-Efficacy (GSE)

Perceived self-efficacy is important to psychosocial functioning and may affect different health outcomes^{99,115}. Perceived self-efficacy can be domain specific or a more general trait^{116,117}. In the latter it is understood to be a state of global confidence in being able to cope across a wide range of challenging or novel situations^{116,117}.

The concept of perceived self-efficacy has its origin in social-cognitive theory advanced by Bandura (1977), and is an important factor for expression of personal behaviour⁸². Bandura defines perceived self-efficacy as: *'beliefs in one's capabilities to organize and execute the courses of action required to produce given attainments'* (page 3)¹¹⁸. To be able to act in certain ways to produce a desired effect, one needs to believe in having the power to make it happen. Four sources contribute to the development of self-efficacy: (1) personal mastery experience, (2) vicarious experience by observing and modelling others' success, (3) verbal persuasion from others that one is capable, and (4) influence from physiological and emotional states^{82,119}.

3. Previous research

HRQoL measures and various measures of symptoms have been used when assessing long-term health outcomes after EP birth. The results obtained from using these measures to study preterm-born populations have usually been compared to results from those obtained from some form of control group(s) or general population norms. For the present work, a systematic literature search was performed in June 2014 and February 2015 to review the scope of measures employed previously; this was done with the assistance of staff at the University of Bergen Library. In addition to studies of EP born and extremely low birth weight (ELBW) children, we included studies also of subjects with very low birth weight (VLBW) or subjects who were very preterm born. We used this approach, because subject inclusion criteria in this research domain are inconsistent across different studies.

The findings are listed below under the headings 3.1 to 3.3 and summarized in 3.4.

3.1 HRQoL after preterm birth in childhood through adolescence to young adulthood

Traditionally, various generic measures of HRQoL have been used, and there has been a variety of instruments employed in the existing literature, which is rather limited. No disease-specific measures have been developed for use in children born preterm.

3.1.1 Physical well-being

Parents have reported inferior physical well-being in their school-aged children born very preterm or EP or with ELBW in the late 1970s and in the late 1990s compared to TB children¹²⁰⁻¹²². Others have reported similar physical well-being¹²³. One study found similar self-reported general health at 8 years of age¹²⁴. When assessing their children in adolescence, parents have reported poorer mobility¹²⁵ or similar mobility¹²⁶, poorer physical functioning and global health¹²⁷ or similar physical functioning, but poorer general health for their preterm-born children¹²⁸. The presence of pain in

this population was reported to be similar to that of the control group^{121,125,128}. Adolescents have self-reported similar physical well-being¹²⁸⁻¹³⁰, and general health^{124,128}, but also poorer physical functioning^{131,132} and mobility¹²⁶. Self-reports of pain have been similar¹²⁸⁻¹³⁰ or better¹²⁶. As adults, preterm or ELBW children have generally self-reported similar or better physical functioning, general health, and less pain¹³³⁻¹³⁷. However, preterm-born males have also reported inferior physical functioning¹³⁸⁻¹⁴⁰.

3.1.2 Emotional well-being

When assessing their preterm-born children at school age, parents reported similar emotional well-being for their children like parents of TB children¹²¹⁻¹²³, but in terms of self-esteem or body image, there were conflicting findings^{122,123}. Three studies employing parents' reports of their children in adolescence concluded that there was no difference in emotional status^{125,126,128}, however, Indredavik et al. (2005) reported inferior self-esteem and behaviour¹²⁸. Adolescents give an impression of similar emotional well-being when referring to self-esteem, emotions, vitality and behaviour^{126,128-130,132}. One study, however, reported inferior psychological well-being, moods and emotions, and self-perception¹³¹. At large, preterm-born adults seem to score relatively similarly to TB peers in all features concerning emotional well-being^{133,134,138,139}. Although, a few studies have demonstrated inferior mental health in this population when assessed in adulthood^{135-137,140}.

3.1.3 Social well-being

The few studies that have assessed social well-being when preterm children reach school age (by parental report) indicate that this aspect of development is inferior in terms of relationships formed with friends compared to TB children^{122,123}. Limitations in schoolwork and activities with friends due to physical health were reported by parents when children were adolescents¹²⁷. Similar characterizations of social well-being were reported by adolescents in self-reports^{131,132}. When reaching adulthood, they reported generally similar social well-being in terms of social functioning and

role functioning related to emotional state^{134,135,137-140}. However, one study reported inferior social well-being¹³⁶.

3.1.4 Parental and family well-being

Relationships or well-being towards family of preterm children were similar to TB children during school age, according to parental reports^{122,123}. In adolescence, family activities are affected, and there is a large impact on the parents due to the child's impaired health^{127,128}. When adolescents self-report, they state there are no differences in family well-being¹²⁸.

3.1.5 Factors influencing HRQoL

There is little knowledge about factors that influence HRQoL in preterm-born subjects. Overall, there seems to be poor agreement between parents reports and children's self-reports^{126,128,141,142}. Gender effects have been reported in some studies when assessed at adolescence or adulthood^{128,134,136,138-140}. Poor cognitive functioning and behavioural problems are associated with impaired HRQoL at school age^{122,123} and in adolescence¹⁴³. Such problems at 8 years of age predicted poorer self-reported HRQoL in adolescents who were born preterm without disabilities¹²⁶.

Assessments of neonatal factors in relation to HRQoL are limited. One study found inferior physical functioning at 20 years of age, which could be explained by GA less than 30 weeks, ELBW, mechanical ventilation used, BPD, and IVH¹³⁴. One study found no differences in HRQoL in school-aged children with or without BPD¹⁴⁴. Although the presence of handicap (cerebral palsy, ADHD, or IQ <70) results in poorer physical functioning reported at adulthood¹³⁴ and affects role functioning and family and parents in adolescence¹²⁷, it seems to be inconsistent¹⁴⁵.

In one study, socioeconomic status was reported to affect family well-being in childhood¹²³, while in adulthood, parental education was not associated with inferior HRQoL¹³⁴. It was, however, related to other aspects of health and well-being¹⁴⁶. Depression in adulthood is associated with poorer HRQoL¹⁴⁵.

3.1.6 Developmental changes in HRQoL

One study showed that self-reported global health from 8 to 14 year old ELBW children born 1992-1995 declined slightly in both preterm and TB children ¹²⁴. We identified three studies that investigated development using a HRQoL measure from adolescence to adulthood in preterm children born around the 1980s. These found a minor decline in HRQoL ^{137,143,145}, and this was similar to HRQoL of TB children when assessed as adults ¹⁴⁵.

3.2 Emotional and behavioural difficulties

In contrast to HRQoL, behavioural issues of preterm-born children have been studied more extensively, especially at younger ages. Studies using similar “*Achenbach System of Empirically Based Assessment instruments*” (ASEBA), as we did in the present work, are listed next.

Two major meta-analyses of studies done on children born very preterm or with VLBW reported increased behaviour problems compared to TB children. They assessed the children with the CBCL from 5 years of age to late adolescence and showed that they experienced, in particular, increased internalizing and externalizing problems ¹¹, and were aggravated with attentional problems ¹⁰. In a recent meta-analysis of 11 to 20 year old subjects born with VLBW or very preterm (< 32 weeks GA), a doubled risk for developing anxiety problems was found compared to TB controls ¹⁴⁷. Similar patterns of behavioural problems and attention, social, and thought problems were found in school-aged children from four different countries across two continents who were born with ELBW in 1977-1987 ¹⁴⁸. In a Swedish review of different cohorts of children born EP or with ELBW or VLBW between 1984 and 1992, increased rates of general behavioural problems were identified; internalizing, attention, thought, and social problems were also present ¹⁴⁹.

3.2.1 Childhood and adolescence

Studies of various birth cohorts and degrees of prematurity have reported increased behavioural problems in preterm-born children^{148,150-157}. In mid childhood, internalizing behaviour (anxiety/depression, withdrawal, and somatic problems) and attention problems were especially present in some, while externalizing behaviour seemed to be less pronounced^{151,155-157}. Social problems and cognitive problems have also been reported at this age^{148,151,157}. Several studies have reported increased behaviour problems in adolescence of both the internalizing and externalizing kind, as rated by parents^{153,154,158}. Researchers have also noted similar externalizing behaviour¹⁵⁰, as well as similar behaviour in general compared to peers¹⁵⁹. Self-reports of behaviour have in general demonstrated that preterm-born adolescents perceive themselves similarly to peers or even better^{150,154,159,160}. In a recent report, teenagers who were born with ELBW had increased problem scores in every Youth Self-Report scale, except for rule-breaking behaviour¹⁵².

3.2.2 Young adults

Few studies have followed preterm-born individuals to young adulthood. Two studies used ASEBA instruments, which identified relatively similar self-reported behaviour as peers, especially for males, while females perceived overall more problems and internalizing problems, in accordance with the parents' reports^{161,162}.

3.2.3 Factors influencing emotional and behavioural difficulties

An inverse relationship has been found for BW and GA and degree of behavioural problems^{10,163}. There seems to be inconsistency in the effect of gender on these problems in childhood and adolescence^{145,150,151,154}, but in late adolescence males were reported to have more problems¹⁵³, and in young adulthood, females had more problems^{161,162}. The finding of behavioural problems persisted after exclusion from the analysis of adolescents with neurologic impairments¹⁶⁴. Sociodemographic and environmental factors have been associated with behavioural outcomes, but the importance of this relationship is not clear^{142,150,151,154,164}. Neonatal factors have been

associated with later-appearing behaviour outcomes: increased internalizing problems at 7 years of age were associated with a higher number of skin-breaking procedures or morphine exposure ¹⁶⁵.

3.2.4 Developmental changes in emotional and behavioural difficulties

Some studies have followed development of behaviour in preterm-born children across ages. A recent study of a regional VLBW population born in the late 1990s demonstrated increased attention and social problems both at 7 and 9 years of age ¹⁵⁷. Both ELBW and very preterm children born in the 1980s showed persistent or increased parent-reported behaviour problems from early to middle-school age ^{156,166,167}. ELBW individuals born around 1980 had increasing internalizing problems from adolescence to young adulthood ^{168,169}. A tendency of more mental health problems from 14 to 20 years of age was found in a Norwegian VLBW population born in the late 1980s ¹⁷⁰. Problems identified in childhood or adolescence meant that there is an increased likelihood for problems to be expressed in young adulthood ¹⁶⁹.

3.3 Pain

Studies investigating possibly long-term effects of neonatal pain in preterm-born children within the age categories of interest for this thesis work were sparse. For this reason, pain studies of preterm-born children of various age categories, TB children with exposure to the NICU, as well as some older children have been included for comparison purposes. The studies are characterized by low sample sizes.

3.3.1 Pain symptoms and stress regulation

Early studies of children born with ELBW and assessed as toddlers reported that they were less sensitive to everyday pain compared to TB control children, as assessed by their parent ¹⁷¹. They also displayed more somatization; i.e., more somatic complaints of unknown origin at 4.5 years of age according to their parents ¹⁷². The tendency of increased somatization in those children was absent in self-reports in early school

ages and in late adolescence^{153,173}. This is consistent with other studies of VLBW and EP children born in the 1980s and mid 1990s. While these studies found that their pain sensitivity was altered, they found no increased self-reported pain in middle childhood or adolescence,^{174,175}. Grunau et al. (2013) reported an association of cumulative neonatal pain-induced stress with altered basal cortisol levels (in saliva and hair) measured at different time points through childhood¹⁰⁹. Low levels were found in the neonatal period, up-regulation occurred at 8 and 18 months, and down-regulation occurred at 7 years of age^{109,113,176}. At 7 years of age cortisol response (in saliva) and diurnal levels was predicted by neonatal pain-related stress, such as skin-breaking procedures, with boys possibly more affected¹¹¹.

3.3.2 Pain sensitivity

Eleven-year-old EP-born children (< 26 weeks GA) had reduced general thermal sensitivity for both hot and cold perception compared to matched TB controls; this decreased sensitivity was even more pronounced in those that had undergone neonatal surgery¹⁷⁵. Nine to 14 year old children who were preterm-born (≤ 31 weeks gestation) and TB children who had received NICU treatment displayed an altered response to painful thermal stimulation compared to full-term control children. More specifically, this was a greater perceptual sensitization to tonic heat (prolonged pain stimuli) in the presence of an elevated heat threshold¹⁷⁷. When habituation to thermal pain was tested, both preterm and TB children who had received NICU treatment habituated less compared to the control children¹⁷⁸.

Nine- to 12-year-old children who were both EP-born and TB and who had undergone cardiac surgery in the neonatal period displayed reduced global sensitivity to touch compared to matched TB control children¹⁷⁹. The neonatal scar area of the children was also hyposensitive to touch and thermal stimulation compared to the non-injured sites¹⁷⁹. When assessing tenderness in 12 to 18 year old children born at a GA < 35 weeks or BW < 1500 grams, more tender points and lower tender threshold were found compared to TB peers¹⁷⁴. Children exposed to burn injuries at 6

to 24 months of age displayed alterations in sensory and pain processing at 9 to 16 years of age, with different patterns connected to the severity of the burn injuries¹⁸⁰.

3.4 Summary of past research

Available knowledge on HRQoL and behaviour in EP-born subjects is based principally on cross sectional studies, largely from the early neonatal era, and the knowledge on longitudinal developmental patterns is limited. Parents of EP-born children perceive, in general, their children's HRQoL and behaviour to be inferior to term-born children. When reaching adolescence and young adulthood, self-reports of HRQoL and behaviour tend to be relatively similar for EP-born and TB peers, however there is some indication of poorer psychosocial HRQoL among EP-born young adults. There is some evidence that early pain experiences can impact later pain responses, but the data is conflicting.

4. Aims of the study

The overall aim of this thesis work was to investigate how EP birth affects health and well-being of the individuals as they progress through childhood and early adulthood. We assessed this by comparing EP-born subjects' developmental trajectories of HRQoL and emotional and behavioural patterns, and their perception of and responses to pain to that of matched TB control subjects. The specific aims were as follows:

- **Paper I.** To investigate whether HRQoL of 10 year old children born EP in 1991-1992 differed from HRQoL of children born at term. We also aimed in this study, to investigate how perinatal and neonatal morbidity and current clinical and sociodemographic characteristics affect HRQoL in these children.
- **Paper II.** To investigate whether pain tolerance, pain perception, and subjective health complaints in adolescents born EP in 1991-1992 differed from that of TB control peers. To explore possible associations between sociodemographic, personal and neonatal factors and the pain experience.
- **Paper III.** To investigate whether development of HRQoL and emotional and behavioural difficulties differ by gender in 10 to 18 year olds born EP in 1991-1992 compared to TB peers, as reported by their parents. We also aimed in this study to determine how early behavioural problems affect the development of HRQoL. Other aims were (1) to investigate whether self-reported HRQoL and emotional and behavioural difficulties at 18 years of age differed from TB peers, (2) whether perceived self-efficacy was associated with outcome, and (3) whether there were associations between neonatal variables and outcome at 18 years of age.
- **Paper IV.** To investigate whether the development of HRQoL and subjective health complaints from late adolescence to young adulthood in individuals born EP in 1982-1985 differed from those of matched TB peers.

5. Materials and methods

5.1 Design

This thesis work was a population-based longitudinal matched controlled study of two cohorts of children born EP in 1982-1985 and 1991-1992; matched control TB children from the same time periods were recruited for comparison. These groups were assessed twice within a seven-year period. EP-born children were enrolled at the first measurement point (i.e., in retrospect regarding the exposure) and followed prospectively to the second follow-up. In papers I and II, the design was cross-sectional; in paper III, the design was both cross-sectional and longitudinal; and in paper IV, the design was longitudinal (Table 2).

Table 2. Summary of relevant experimental details for papers I-IV.

Paper	Participants	Design	Method	Statistical analyses	Main outcome measures
I.	<ul style="list-style-type: none"> Extremely preterm-born in 1991-1992 Matched term-born controls 	<ul style="list-style-type: none"> Cohort, case-control Cross-sectional 	<ul style="list-style-type: none"> Questionnaires: Parent report	<ul style="list-style-type: none"> Cronbach's alpha Paired sample t-test McNemars test Linear regression model Mixed linear regression model 	<ul style="list-style-type: none"> HRQoL subscales and summary scores by the Child Health Questionnaire
II.	<ul style="list-style-type: none"> Extremely preterm-born in 1991-1992 Matched term-born controls 	<ul style="list-style-type: none"> Cohort, case-control Cross-sectional 	<ul style="list-style-type: none"> Cold Pressor Task Questionnaires: Self-report 	<ul style="list-style-type: none"> Kaplan-Meier with log-rank test Cox regression (clustered) Wilcoxon 	<ul style="list-style-type: none"> Pain tolerance Pain intensity Health Behaviour in School-aged Children: somatic, psychological and

				signed rank test • Mixed linear regression model	total scores
III.	<ul style="list-style-type: none"> • Extremely preterm-born in 1991-1992 • Matched term-born controls 	<ul style="list-style-type: none"> • Cohort, case-control • Longitudinal • Cross-sectional 	<ul style="list-style-type: none"> • Questionnaires: Parent-report Self-report 	<ul style="list-style-type: none"> • Mixed linear regression model • Generalized logistic regression model • Linear regression model 	<ul style="list-style-type: none"> • HRQoL subscales of the Child Health Questionnaire • Child Behaviour Checklist and Youth Self Report-scales
IV.	<ul style="list-style-type: none"> • Extremely preterm-born in 1982-85 • Matched term-born controls 	<ul style="list-style-type: none"> • Cohort, case-control • Longitudinal 	<ul style="list-style-type: none"> • Questionnaires: Self-report 	<ul style="list-style-type: none"> • Chi-square test • One-way ANOVA with post-hoc tests • Mixed linear regression model 	<ul style="list-style-type: none"> • HRQoL subscales of the Child Health Questionnaire and Short-Form Health Survey • Health Behaviour in School-aged Children: somatic and psychological scores

5.2 Study population

5.2.1 Preterm-born population

The inclusion criteria for subjects of this group were either $GA \leq 28$ weeks or $BW \leq 1000$ grams for neonates born of mothers living within two counties of Western Norway (Hordaland and Sogn og Fjordane) at the time of delivery. The NICU at Haukeland University Hospital was and still is the only unit caring for the sickest newborn infants in this region of Western Norway. The first cohort consisted of survivors born from January 1982 through December 1985. These subjects were thus born before the introduction of surfactant and prenatal steroid use for preterm

children. The participants of the second cohort were born from January 1991 through June 1992, after the implementation of new intensive care neonatology procedures.

At the time of this thesis work, the NICU at Haukeland University Hospital had an annual birth rate of approximately 6700. Of the included EP-born children, all except for five were born at the maternity ward. Candidates for inclusion were identified through the NICU's admission protocols. To avoid misclassification of GA, two independent investigators reviewed all charts of neonates with BW < 1750 grams and GA < 32 weeks, a total of 346 charts. With information from the obstetric and paediatric charts, the GA set by admittance was reassessed. The algorithm of Yudkin¹⁸¹ was applied both at the neonate's admission to the NICU and at the retrospective reassessment. GA at birth was principally set according to the last menstrual period (LMP) as reported by the mother on the pregnancy charts (tabulated data). Delivery date set by the LMP were compared with that obtained from ultrasound scans performed before 21 weeks gestation, and with postnatal paediatric examination according to the method proposed by Ballard¹⁸². If scan assessment differed by more than two weeks from the estimate based on LMP, the scan estimation was preferred and used. The paediatric assessment was preferred if it differed by more than four weeks from the LMP estimate or the ultrasound scan. In 9 of the 346 reviewed charts, the GA was difficult to determine, and therefore the decision to assign GA was entrusted to an obstetric expert on foetal medicine and intrauterine development.

To ensure that eligible children were alive before enrolment, the National Population Register was consulted. Furthermore, relevant knowledge of their medical status was obtained from local hospital charts, and in some cases paediatric neurologists were consulted. Except for severely disabled EP-born subjects that were approached carefully by telephone, a standardized letter was used to invite all other candidates for participation. Fifty-one persons were eligible from the first birth cohort, and 35 for the second birth cohort. Of the 51 eligible subjects from the eldest birth cohort, 2 were inaccessible (one living abroad, one never responded), and 2 refused to participate, one was excluded due to a severe cardiac condition, leaving 46 available for participation. All 35 from the youngest birth cohort accepted participation.

5.2.2 Term-born control subjects

Using the birth protocols in the obstetric department, we identified TB control children by selecting the temporally nearest TB child of the same gender with BW between 3000 and 4000 grams; these weights were within the 10th to 90th percentile of all Norwegian births for the time period of interest¹⁸³. If the first contacted control candidate declined participation, the next one on the list was approached, and so on until a matched TB control child was found. Our intention was to recruit a control child who was matched on two important variables in developmental research: age and gender. Even though there is a known socioeconomic disadvantage associated with preterm delivery¹⁸⁴, this indicator was not used in the process of matching the control children. An independent secretary performed the searching and inclusion process.

One exclusion criterion was a candidate having a home address greater than one-hour transport by car to Haukeland University Hospital; this was done for practical and financial reasons. It was considered unlikely that this would produce any sample-selection bias. The other exclusion criterion was a candidate having a diagnosis of mental or physical disability that would likely interfere with the testing situations. Only one such child was identified who had a serious lung condition later requiring a lung transplant.

Using this inclusion process, an average of 1.3 TB children had to be approached per EP-born index child in order to complete a full 1:1 matched control group.

5.3 Data collection

This thesis work was part of a larger study that took place at the Department of Paediatrics at Haukeland University Hospital at the Cardio-Respiratory Laboratory, principally assessing lung function and exercise capacity. All participants were examined by the same paediatrician on both follow-up occasions and were seen twice within two weeks at the first study period in 2001/2004. At the second period in 2008/2010, nearly everyone was seen twice within a two-week time period; however,

some individual adjustments had to be made. At first follow-up, participants of both cohorts and the accompanying parent completed the questionnaires at the test site on the first test day. This applied also for the second follow-up; however, several parents did not accompany the child, and instead completed the questionnaires at home. This was either returned to the research team by the adolescent or by mail (10 EP-born parents and 19 control parents). Some of the EP-born and TB subjects completed the questionnaire at home as well (5 EP-born and 3 TB). The parents of the 1982-1985 cohort when seen at 24-25 years of age did not attend the second follow-up and did not contribute to the second investigation.

5.3.1 Health-Related Quality of Life measures

Two age-appropriate generic measurement instruments with good psychometric properties were chosen for the purpose of this thesis.

Child Health Questionnaire (CHQ)

The primary objective of the authors of the CHQ was to develop '*general functional status and well-being instruments for children age five or older*' (p. 28) ¹⁸⁵. The theoretical framework for the development of the questionnaire was based on WHO's definition of health, which incorporates both physical and psychosocial dimensions. These are important issues when assessing well-being in children, according to the originator of the instrument ¹⁸⁵. These instruments were developed for subjective assessment of functioning in relation to health, emotional, and social well-being in children and adolescents, either by self-reports or by parental reports ¹⁸⁵. The CHQ scales address domains of HRQoL within the subscales of physical functioning, role/social functioning in relation to physical, emotional and behavioural constraints, general health, bodily pain, self-esteem, mental health and behaviour, impact of the child's health on family activity, and cohesion (Table 3, Figure 1). The parent form also assesses impact on parents in terms of time available for themselves and emotional strain. Responses are scored along a 4 to 6 point Likert-type scale using a recall period of the preceding four weeks. An exception is the scales of *General Health* and *Family Cohesion*, which have no recall period, and the *Change in Health*,

which uses *'last year'* as the recall period. However, it should be noted that the latter scale was not included for this thesis work. Within each subscale, items are summarized, and scores are transformed into scales ranging from zero to 100, with higher numbers representing better functional health and well-being.

The CHQ-Child Form 87 is for self-completion for subjects aged 10 to 18 years and consists of 87 items covering 12 subscales. The CHQ-Parent Form 50 is for use with children aged from 5 to 18 years and consists of 50 items that cover 13 subscales. Two summary measures cover the physical and psychosocial component of 10 of the subscales (Figure 1). These summary measures are standardized based on scores obtained from general and clinical sample populations (from the USA) and are transformed to a T-score. The standardized scale has a mean of 50 and a standard deviation (SD) of 10. Validated Norwegian versions of the CHQ-Child Form 87 and CHQ-Parent Form 50 were used for this thesis work^{186,187}.

Short-Form Health Survey (SF-36)

The 36-item Short-Form Health Survey (SF-36) was developed to measure functional health and well-being from the patient's point of view^{188,189}. This is a frequently used instrument that assesses eight domains of health within the subscales of physical functioning, role limitations due to physical health problems or emotional problems, bodily pain, social functioning, mental health, vitality (energy level and fatigue), and general health perception (Table 3)¹⁸⁹. The Norwegian version has demonstrated acceptable psychometric properties¹⁹⁰, and version 1.1 was used in the present. Except for the two role functioning scales, which have dichotomized response choices, the responses are scored along a 3 to 6 point Likert-type scale, with the preceding four weeks used as a recall period. An exception is the two scales of physical functioning and general health which refer to the present. The scores are transformed and summarized into scales ranging from zero (poorest) to 100 (optimal). Also for this instrument, two summary scores may be calculated: the physical and mental component summary scores, but were not used for this thesis work.

5.3.2 Emotional and behavioural difficulties

We used Achenbach's system of empirically based instruments that were developed to assess diverse aspects of adaptive and maladaptive functioning in a child from multiple sources⁸⁴. It is a well-established instrument with good psychometric properties, also for the Norwegian version^{88,191}.

Child Behaviour Checklist (CBCL) and Youth Self-Report (YSR)

CBCL 4-18 (year 1991) parent-form version and YSR 11-18 for self-completion (2001) version were used. For the problem items, the responses are scored along a scale ranging from 0 (not true) to 2 (very often or often true), with the preceding six months used as a recall period (Table 3). The problem items are summarized to arrive at a *total problem* score and according to eight syndrome scales: withdrawn, anxious/depressed, somatic complaints (summarized to a global scale of *internalizing problems*); rule-breaking/delinquent behaviour and aggressive behaviour (summarized to a global scale of *externalizing problems*); and social, thought, and attention problems. Higher scores on these scales represent more problems in the child. The competence scales consist of 20 items, which assess the amount and the quality of participation in organized activity, sports, hobbies and jobs, and connection with family and friends, and school performance. From these items, activity, social, school, and total competence scales are calculated, with higher scores indicating better competencies.

5.4 Health Behaviour in School-Aged Children—Symptom Checklist

The Symptom Checklist instrument measures subjective health complaints, using eight symptom items of somatic and psychological character (Table 3). It was originally developed for a WHO cross-national survey of health in European populations of adolescents, with the aim of increasing knowledge and understanding of the lifestyle and health behaviour of young people¹⁹². A validated Norwegian version was used in this thesis work^{193,194}. The items assess an individual's frequency

of experiencing abdominal pain, headache, back pain, dizziness (somatic subscore), feeling low, nervousness, irritability, and difficulties falling asleep (psychological subscore). The items are scored along a 5-point scale from 0 to 4, with 0 representing ‘rarely or never’ and 4 representing ‘about every day’. All items refer to experiences in the previous 6 months as the recollection period (Table 3). The scores are summarized to produce an overall sum-score range, with possible scores ranging from 0-32 and subscores that could range from 0-16.

5.5 Pain experiment

We chose the Cold Pressor Task (CPT) as the paradigm for assessing pain perception. The method has been widely used for evaluation of both experimental and chronic pain, is simple to apply, and is without risks when following the stated guidelines^{195,196}. It creates an aching-type of pain that is completely reversible in a few minutes after the limb is removed from the ice water. With the CPT, it is possible to measure pain threshold, tolerance, and intensity, but we measured only pain tolerance and intensity in the work done for this thesis. Pain is considered to arise quite immediately and the actual pain threshold may be difficult to evaluate, and was therefore not included.

We followed the guidelines for the CPT^{195,196}, and used a simple device for the experimental setup. A plastic tank of water was filled with crushed ice, which at stabilization, the temperature ranged from 0 to 2°C. The ice and resulting liquid water were mixed thoroughly immediately before the test, and the temperature was controlled when mixed and immediately after the test. Every participant was informed in the same manner by written information and orally by the researcher (BJV). They were instructed to immerse their right hand into the ice water to the level of the wrist, palm facing down, and to hold it submerged until pain become intolerable. Every 30 seconds they were requested to rate the perceived pain on a numeric rating scale (NRS). They were not informed that the test would be terminated after 3 minutes. The test was performed in the same manner by the same researcher for all subjects.

Testing was completed in a separate room with only the researcher present, located behind the subject. Only one test was performed.

5.6 General Self-Efficacy

GSE was assessed by using a five-item scale version of the original 10-item scale. The original scale has demonstrated good psychometric properties in cross-national studies, also in Norwegian studies. This confirms that the construct is universal and one-dimensional^{116,117,197,198}. The subjects' level of agreement was requested on a four-response category scale, with 1 meaning completely disagree to 4 meaning completely agree (Table 3).

5.7 General questionnaire

Custom questionnaires were developed with validated questions from Norwegian population studies^{192,199,200} to be applied in both cohorts at both measurement points in order to include other social and demographic areas. These questionnaires may be obtained from the author.

Table 3. Summary of measurements

Questionnaire	Forms	No. of items		
CHQ scales:			Low score ^a	High score ^a
Physical functioning	CF87 PF50	9 6	Limitation in performing physical activities and self-care due to health	No limitation in performance of physical activities or self-care
Role/social physical	CF87 PF50	3 2	Limitation in schoolwork or activities with friends due to physical health	No limitation in schoolwork or activities with friends
Role/social emotional ^b	CF87 PF50 ^b	3 ^b	Limitation in schoolwork or activities with friends due to emotional problems	No limitation in schoolwork or activities with friends
Role/social behaviour ^b	CF87 PF50 ^b	3 ^b	Limitation in schoolwork or activities with friends due to behaviour problems	No limitation in schoolwork or activities with friends

Bodily pain	CF87 PF50	2 2	Extremely severe, frequent, and limiting bodily pain	No pain or limitations due to pain
Behaviour	CF87 PF50	17 6	Frequently exhibition of aggressive, immature, delinquent behaviour	No aggressive, immature, delinquent behaviour
Mental health	CF87 PF50	16 5	All the time feelings of anxiety and depression	All the time peaceful, happy, and calm
Self-esteem	CF87 PF50	14 6	Dissatisfaction with abilities, looks, family/peer relationships, and life overall	Satisfaction with abilities, looks, family/peer relationships, and life overall
General health	CF87 PF50	12 6	Health is poor and is likely to get worse	Health is excellent and will continue to be so
Parental impact - emotional	PF50	3	Excessive emotional worry/concern due to child's physical and/or psychosocial health	No feelings of worry/concern about child's health
Parental impact - time	PF50	3	Limitations in time available for personal needs due to child's physical and/or psychosocial health	No personal time limitations
Family activities	CF87 PF50	6 6	Child's health limits/interrupts family activities or creates family tension	Child's health never limits/interrupts family activities nor creates family tension
Family cohesion	CF87 PF50	1 1	Poor ability for the family to get along	Excellent ability for the family to get along
ASEBA:			Scoring	
Competence scales:			Higher scores indicate better competence ^c	
Total competence	CBCL YSR	20 17	Summation of 0-1-2 scale (0-1=0, 2=1, 3=2)	
Activities			Summation of 0-1-2-3 scale	
Social				
School/academic ^d				
Problems/syndrome scales:	CBCL YSR	118	Higher scores indicate more problems ^c	
Anxious/depressed			Summation of 0-1-2 scale	
Withdrawn/depressed				
Somatic complaints				

Social problems	CBCL YSR		Total problem score range 0-236 Total problem score range 0-210
Thought problems			
Attention problems			
Rule-breaking or delinquent behaviour			
Aggressive behaviour			
Internalizing			
Externalizing			
Total problems			
SF-36 scales:			Summation and transformation of items to eight 0-100 scales. 0 = worst possible health state 100 = best possible health state
Physical functioning		10	
Role limitations, physical		4	
Bodily pain		2	
General health perception		5	
Vitality		4	
Social functioning		2	
Role limitations, emotional		3	
Mental health		5	
GSE scale		5	Scoring 1-4, summation and calculating of the mean. Higher scores indicate better self-efficacy.
HBSC-Symptom Checklist			Scoring 0-4, summation with higher scores indicating more complaints.
Somatic subscale		4	Range 0 – 16
Psychological subscale		4	Range 0 – 16
Total		8	Range 0 - 32

^aScoring range 0 to 100.

^bThe role/social-emotional, and role/social-behaviour are combined into one scale in the CHQ-PF50.

^cRaw scores from computer-scored competence and syndrome profiles.

^dThe YSR - academic performance scale and CBCL- school scale are not analogous.



Figure 1. CHQ measurement model from Landgraf¹⁸⁵.

5.8 Pulmonary function and current diagnoses

Current pulmonary function was quantified by FEV₁, which was measured with a Vmax 22 spirometer (Sensor Medics, Anaheim, CA, USA). The subjects' values were transformed to percentages predicted by a standard reference equation²⁰¹. Asthma was diagnosed according to self-report of wheeze in the last 12 months, plus either 'asthma ever' or asthma medication in the last 12 months.

The same paediatrician (TH; Professor Thomas Halvorsen) obtained the medical history and a standard physical examination at both occasions from all subjects. Relevant medical information was available from hospital records for both EP and TB subjects. Information on current established diagnoses was also obtained from the parents at the time of examination, or from the medical records in cases of uncertainty.

5.9 Neonatal data

Except for one preterm-born participant, patient records (obstetric and paediatric) were available for all subjects. For this single preterm participant lacking records, we used information from discharge records and what the mother recalled. Most data were in standardized or tabulated forms, and the following data were recorded: BW, GA, SGA < 10th percentile, presence/absence of maternal infection, use of antenatal or neonatal corticosteroids, presence/absence of cerebral haemorrhage, days of mechanical ventilation, severity of BPD (none, mild or moderate/severe), duration of oxygen treatment, days of mechanical ventilation, number of painful events, number of administered doses of intravenous analgesics (morphine), and use of sedatives (benzodiazepine). At the time these EP-born children were treated in our NICU, morphine was administered as a bolus during mechanical ventilation (0.1-0.2 mg/kg) up to six times/day for the first two days after intubation and thereafter, by clinical judgment. Benzodiazepine (Stesolid) was administered by clinical judgment (0.25 mg/kg), up to six times/day. Painful events were defined as injections, placement of venous or arterial cannula or central venous catheters, heel pricks, insertion of chest-drain tube, endotracheal intubations, nasal and endotracheal suctioning (estimated to be three per day when a tube was present) and surgical interventions.

5.10 Statistical methods

As a rule, paired statistics were applied, because we used matched samples. Based on the sample size (around 60 subjects) we assumed that the estimated differences were approximately normally distributed, which permitted the use of parametric methods.

For most statistical evaluations we used SPSS (Statistical Package for the Social Science, Chicago, USA). For specific other analyses for Papers II and IV, we used the statistical program R (the R Foundation for Statistical Computing, Vienna, Austria). We used McNemar's test in StatXact for certain analyses of Paper I. For analyses in which we used paired and longitudinal designs, the mixed linear model was applied; this allowed us to take into account contribution from pairs with declines and missing values²⁰². In this model, adjustment for correlated measures within pairs was performed. For the group born EP, when testing for possible associations of neonatal variables on the outcome variables, simple linear regression analysis was applied. The significance level was set at $p \leq 0.05$, indicating that the observed differences could have occurred by chance alone in less than 5% of the tests.

Paper I. For categorical and continuous variables the McNemar's test and t-test for paired samples were used. Results are presented as proportions or means with standard deviations (SD), or as odds ratio with 95% confidence interval (CI), when appropriate. Group comparisons on the CHQ-PF50 scales were performed both with the Wilcoxon signed rank test and paired t-test; results are presented as mean differences with 95% CI. These were graphically displayed according to group and gender. In the mixed linear regression model, potential confounding variables were evaluated, and we also tested for interaction effects of gender and learning/attention problems with regard to the group differences evaluations.

Paper II. The Wilcoxon signed rank test was used for comparison of scores on the HBSC and GSE of the two groups. Their data are reported as medians with 25 and 75 percentiles stated. Pain intensity in the groups was reported as means for overall NRS scores, NRS for each of the 6 measurement points and NRS at test termination. Comparisons between groups were made with paired statistics. Kaplan-Meier survival curves were used with the log rank test for testing time from immersion to withdrawal from the ice water; i.e. pain tolerance expressed as seconds in ice water. Kaplan-Meier survival curves were also constructed for between group comparisons in relation to demographic variables. They were also used to analyze differences within EP-born participants as a function of neonatal variables. In the EP-born group,

separate adjusted (gender and GSE score) Cox regression analysis was used to test the effect of days of mechanical ventilation, doses of morphine, and number of pain events on pain tolerance employing a quadratic term in addition to examining the linear relationship. Unadjusted and adjusted clustered Cox regression analyses were performed to test differences of pain tolerance between the two groups; these are reported as hazard ratios with 95% CI.

Paper III. For comparisons between the two groups on the sociodemographic variables, binary and ordinal logistic regression analyses with the generalized linear regression model were used. Results are presented as proportions. The mixed-linear regression model was used to compare development from 10 to 18 years between the groups, separated by gender on parent-reported HRQoL and behaviour scores. We also included an interaction term for testing the effect of time by group. Results are presented as differences, with 95% CI stated between groups at 10 and 18 years of age. Adjusted analyses on the HRQoL score changes in the two groups from 10 to 18 years were performed with behavioural problems at 10 years of age as a predictor variable; an interaction term of gender by group was also included. Unadjusted comparisons of self-reported HRQoL and behaviour scores at 18 years were performed with a mixed linear regression model, with sub-analyses done for effects of gender, and adjusted analyses done with gender by group as an interaction term.

Paper IV. The Chi-square test was used for categorical data, and one-way ANOVA analyses were performed for comparisons between groups (EP-born children with and without impairments and TB controls) on the HRQoL scores at 17 and 24 years of age. Post-hoc tests were used for the ANOVAs. Results are presented as proportions and group means. For variance measures, SDs are reported, and differences with 95% CI between EP-born children with impairment and without impairment versus TB controls are presented for the two measurement points. The mixed-linear regression model was used to compare unadjusted and adjusted development on the HBSC scores from 17 to 24 years of age between the groups, and a time by group interaction term was included.

5.11 Statistical power

Preferably, statistical power should be calculated *a priori* in order to confidently detect a true effect by limiting the risk for type II error²⁰³. In this thesis work, an ‘effect’ is understood to be a clinical difference in outcome measures between the EP and TB groups. Within quality-of-life research, changes or differences of 5 to 10 points on a 100 point scale are generally considered clinically significant^{67,185}. The original sample size we believed to be appropriate was calculated based on achieving 90% power to detect differences in lung function (FEV₁ of $\geq 7.5\%$), the original primary outcome variable, between the EP and TB individuals in each of the two birth cohorts at a 0.05 significance level and with a predicted SD of 10%²⁰⁴. For the HRQoL outcomes, *a priori* power calculations were difficult to perform, due to not knowing *a priori* what the distribution of CHQ scale scores for preterm children took at that time. For this reason we performed a *post-hoc* power calculation based on the results for the summary scores in Paper 1.

5.11.1 Possible influencing factors

There is limited knowledge about factors that may influence HRQoL in preterm-born populations. But long-term health outcomes after EP birth may be affected by a number of potential influencing factors¹⁶³. These may act as confounding factors that potentially distort the results. Confounding variables are related both to the independent variables and to the outcome. Age was one such factor, and the matching we did on time of birth controlled for this factor’s confounding influence. Gender was another possible confounding factor, which we also accounted for in the matching process. However, according to the literature of outcomes after preterm birth, it was reasonable to consider gender as an interacting factor with the EP and TB groups^{39,205}. BW and GA are considered to be important for outcomes, but with the present relatively narrow inclusion criteria, the likelihood that these variables would influence outcome was expected to be small.

Inequality in socioeconomic status (SES) is known to be associated with preterm birth, and thus has the potential to impact outcome^{8,39,184}. One way SES can be

assessed is by using a proxy measure: maternal education^{206,207}. However, SES may be related more to paternal education²⁰⁸. We used maternal education to get a proxy measure of SES, consistent with previous research^{134,143,146}.

Little is known about the influence of GSE in EP-born populations, but this feature is known to influence health^{115,209} and HRQoL²¹⁰. Therefore, we included this as a possible influencing factor. Other possible influencing factors included in the regression models were based on results from previous research^{39,211}. These were pre- and postnatal variables; presence/absence of maternal infection, use of antenatal or neonatal steroids, cerebral haemorrhage, severity of BPD, days of mechanical ventilation, duration of supplemental oxygen, number of painful events, doses of morphine, SGA < 10th percentile BW or BW ratio (ratio between BW and the 50th percentile BW), and presence/absence of impairment.

5.12 Ethics

The Regional Committee on Medical Research Ethics of the Western Norway Health Authority approved this follow-up study (i.e., all work conducted for this dissertation). Informed written consent was obtained from all participants and their parents if the participant was younger than 16 years. The medical ethical principles for research in the Helsinki declaration were followed, with a special emphasis on the rights of children involved in research. In the original application to the human subjects committee, the pain experiment was not included for evaluation. The protocol for it was submitted and approved before the second investigation began. All investigations undertaken in this dissertation work were considered free of risks for the participants.

6. Summary of results

The results of the studies presented in this dissertation are found in Papers I-IV. Papers I-III report data obtained from the cohort born 1991-1992, while Paper IV reports data obtained from the 1982-1985 birth cohort. A merged flow chart (Figure 2) and a summary of demographic and neonatal characteristics of the two cohorts are displayed below in this paragraph. As expected, based on the inclusion criteria, the two cohorts were relatively similar, except for their impairments (Table 4). There were some born SGA in both birth cohorts, and three and two subjects, respectively, in the 1982-1985 and 1991-1992 birth cohort were included on BW indications only (Table 5).

1982-1985 birth-cohort

1991- 92 birth-cohort

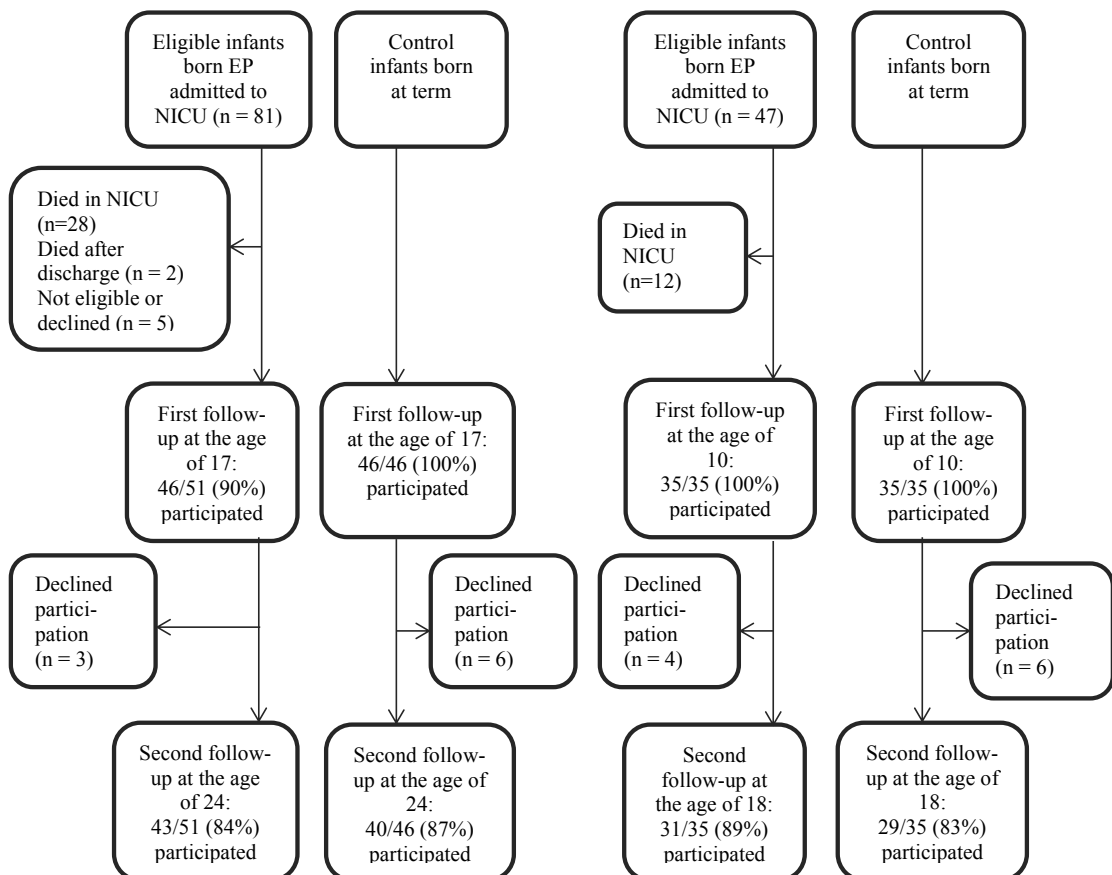


Figure 2. Flow chart showing the number of EP-born and TB birth cohorts from the time of inclusion in our study to age 25 years.

Table 4. Characteristics of EP-born subjects in the two birth cohorts

	1982-1985 cohort (N = 46)	1991-1992 cohort (N = 35)
First measurement:		
age (y), mean (SD)	17.6 (1.2)	10.4 (0.4)
age range	15.3 – 19.8	9.7 - 11.2
Second measurement:		
age (y), mean (SD)	24.7 (1.2)	17.7 (0.4)
age range	22.5 – 26.8	17.0 – 19.3
BW (g): mean (SD)	1014 (192)	933 (204)
range	580 -1480	570 - 1400
GA (wk): mean (SD)	27.3 (1.4)	26.7 (1.7)
Male, n (%)	25 (54)	13 (37)
Neurosensory impairments, n:		
Severe disability	9	0
CP - disabling	4	0
CP - non-disabling	7	0
Wheelchair	3	0
Blind	3	0
Deaf/impaired hearing	2	2
ADHD/ADD ^a		5 ^b
Did not attend second follow-up:	3	4
BW, mean (SD)	1050 (88)	868 (168)
GA, mean (SD)	28.0 (1.8)	26.3 (1.7)
ADHD, n		1
Severe disability, n	1	

^aTwo subjects comorbid with mild mental retardation.

^bOne diagnosed at 14 years of age.

CP, cerebral palsy; ADHD, attention deficit hyperactivity disorder; ADD, attentional deficit disorder; SD, standard deviation; GA, gestational age; BW, birth weight.

Table 5. EP-born subjects according to GA and SGA for the two birth cohorts

GA in weeks	23	24	25	26	27	28	29	30	31	32	Total N (%)
1982-1985 cohort:											
BW \geq 10 th centile	0	0	2	7	12	17	0	0	0	0	38 (82.6)
BW < 10 th centile	1	0	0	1	2	1	0	2	0	1	8 (17.4)
Total by GA: n (%)	1 (2.2)	0 (0)	2 (4.3)	8 (17.4)	14 (30.4)	18 (39.1)	0 (0)	2 (4.3)	0 (0)	1 (2.2)	46 (100)
1991-1992 cohort:											
BW \geq 10 th centile	1	2	4	4	4	11	0	0	0	0	26 (74.3)
BW < 10 th centile	0	1	1	1	3	1	0	1	1	0	9 (25.7)
Total by GA: n (%)	1 (2.9)	3 (8.6)	5 (14.3)	5 (14.3)	7 (20.0)	12 (34.3)	0 (0)	1 (2.9)	1 (2.9)	0 (0)	35 (100)

Figures are counts (% of group): SGA, small for gestational age; GA, gestational age; BW, birth weight.

Paper I. We found that HRQoL measured with CHQ-PF50 at 10 years of age was inferior in the EP-born children compared to TB children in several of the subscales, and especially for psychosocial components and general health. Parents of the EP-born children reported increased strain on the family and parent scales. In adjusted regression models, these differences were related to the EP-born boys for behaviour, social role limitation due to emotional problems, parental strain with emotional worries, and limited personal time due to their child's health. Having learning and/or attention problems were related to inferior HRQoL in all participants, but specifically for EP-born children in the scales of general health and less time available for parents. Adjusting for maternal education level, which was lower for the mothers of EP-born children, did not change the results. Academic deficiencies reported by parents were more pronounced in the EP-born children that had reading and writing difficulties, learning and/or attention problems; that received academic and psychological support; and that displayed below-average school achievement relative to their classmates. Also, EP-born children participated less in physical activities compared to the TB controls. However, their participation in other social activities

was comparable to that of the TB controls. The parents of EP-born children reported inadequate professional support during childhood.

Paper II. We found that adolescents born EP had lower pain tolerance than TB adolescents when they placed their hands in ice water in both the unadjusted and adjusted model. The intensity of pain during this test was similar in these two groups, as were their subjective health complaints. The difference in pain tolerance was related to EP-born males. Subjects who, as neonates, experienced higher levels of pain, were on a ventilator for more days, and who had received more morphine doses were less likely to withdraw their hands from ice water. This association was more pronounced when they were exposed to low dosing treatment. For all adolescents, GSE and high maternal education was positively associated with increased pain tolerance.

Paper III. We found that parents of EP-born boys reported improved HRQoL and behaviour of their child as they progressed from 10 to 18 years of age. Their HRQoL and behaviour approached the level of the TB controls. This improvement was significant for HRQoL within the self-esteem, general health, and the parental impact time scales. For behaviour, it was significant within the total problem scale, internalizing, and anxious/depressed scales. For EP-born girls, who were less inferior to TB girls at age 10, the differences persisted. Having behavioural problems at 10 years of age predicted less improvement in HRQoL in the adjusted model, irrespective of being EP-born or TB. The EP-born adolescents through self-reports showed that they were relatively equal to their TB peers in the unadjusted and adjusted model, both in HRQoL and behaviour. An exception was for the EP-born females, who in the unadjusted gender-specific model reported having lower self-esteem, being more withdrawn, anxious/depressed, and less socially competent compared to the TB females. Adolescents with good GSE were more likely to have better HRQoL and behaviour, irrespective of being EP born or TB.

To illustrate further the results presented in Paper III, an extra table is included here, to show the parent-reported development of their children on CHQ scales mutually

for both genders (Table 6). This demonstrates that the parents of the EP-born subjects tended to give lower scores than the parents of the TB control subjects at both the 10- and 18-year assessments. The scores of the EP-born children tended to improve as they progressed from 10 to 18 years on all scales relative to those of the TB; however, this was significant only for general health and for both scales assessing impact on the parents (group by age interaction). As reported in Paper III the development through the adolescent years was significantly different for the EP born boys for the self-esteem, general health and parental impact-time scales.

Table 6. Unadjusted results for parent-reported CHQ analyses for EP-born and TB children assessed at 10 and 18 years of age

CHQ-Parent Form 50 subscales:	10 years of age				18 years of age				Tests of interaction group by age (p values) ^a
	Preterm (N = 35) Mean (SD)	Term (N = 35) Mean (SD)	Mean estimated difference (95% CI)		Preterm (N = 31) Mean (SD)	Term (N = 28) Mean (SD)	Mean estimated difference (95% CI)		
Physical functioning	95.2 (11.7)	99.5 (1.6)	-4.4 (-8.1,-0.6)		94.6 (11.6)	98.8 (3.2)	-3.9 (-8.0,0.3)		0.87
Role/social - emotional/behavioural	87.0 (23.4)	98.4 (5.5)	-11.4 (-19.6,-3.2)		91.8 (23.5)	97.6 (7.0)	-5.8 (-14.8,3.1)		0.36
Role/social - physical	94.3 (15.6)	98.6 (8.5)	-4.3 (-9.9,1.3)		95.2 (14.4)	98.2 (6.9)	-2.8 (-8.9,3.3)		0.73
Bodily pain	80.3 (21.3)	85.1 (16.5)	-4.9 (-14.2,4.5)		75.7 (26.5)	81.5 (19.7)	-5.2 (-15.6,5.2)		0.89
Behaviour	66.0 (17.4)	79.0 (11.0)	-13.0 (-19.7,-6.3)		77.9 (16.9)	84.0 (13.1)	-5.6 (-13.0,1.8)		0.14
Mental health	76.7 (10.1)	82.4 (7.8)	-5.7 (-10.3,-1.1)		80.3 (13.4)	84.5 (10.5)	-4.0 (-9.0,1.1)		0.62
Self-esteem	70.2 (16.6)	76.8 (10.0)	-6.5 (-13.3,0.2)		71.5 (17.2)	72.6 (14.2)	-0.8 (-8.2,6.6)		0.26
General health	68.0 (22.1)	89.2 (9.2)	-21.2 (-28.2,-14.1)		75.5 (16.8)	85.6 (15.0)	-9.6 (-17.3,-1.9)		0.03
Parental impact - emotional	67.4 (25.2)	88.3 (11.6)	-21.0 (-29.1,-12.7)		77.4 (21.3)	87.2 (13.1)	-8.8 (-17.8,0.2)		0.05
Parental impact - time	85.1 (21.2)	97.5 (6.1)	-12.4 (-17.6,-7.2)		92.5 (11.6)	97.2 (6.5)	-3.2 (-8.9,2.5)		0.02
Family activity	78.8 (24.3)	91.6 (9.1)	-12.8 (-20.3,-5.2)		86.4 (21.4)	92.3 (11.7)	-4.6 (-12.9,3.7)		0.15
Family cohesion	74.9 (20.6)	77.7 (13.6)	-2.9 (-10.9,5.2)		78.5 (17.7)	77.7 (21.8)	1.6 (-7.3,10.4)		0.47

^aFrom mixed linear model: interaction term testing, if analyses of scores of development from 10 to 18 years differed in the EP-born versus the TB group main effect.

CHQ, Child Health Questionnaire; SD, standard deviation; CI, confidence interval.

Paper IV. We found that the EP-born adolescents tested at 17 years of age reported similar HRQoL as their TB peers, with the exception of EP-born subjects with impairments reporting lower physical functioning. In adulthood, the EP-born subjects *without* impairments reported lower HRQoL on the scales of mental health and social functioning and role emotional compared to the TB control subjects, whereas no significant HRQoL differences were observed for EP-born *with* impairments. From 17 to 24 years of age, EP-born subjects *without* impairments reported increased psychological complaints and more than their TB peers in unadjusted as well as adjusted analyses.

Summary of all results. We have investigated how EP birth affects health and well-being as the children progress through childhood and early adulthood. EP-born subjects' developmental trajectories of HRQoL, emotional and behavioural patterns, and their perception of and responses to pain were compared to those trajectories and patterns of matched TB subjects. We found that the parents of the EP-born subjects perceived their children to have poorer HRQoL in nearly all domains in childhood, including the family and parent domains, and to have more emotional and behavioural difficulties compared to the TB controls. In late adolescence, by contrast, these differences were smaller and showed a positive shift towards the patterns of their TB peers. A gender difference was apparent, with EP-born males being more strongly affected in childhood compared to EP-born females. However, EP-born males improved substantially as they progressed through puberty. For all subjects, emotional and behavioural difficulties in childhood predicted a less favourable change in HRQoL through puberty. In adolescence, EP-born children reported that their HRQoL and behaviour and perception of pain was fairly similar to be their TB peers, at the same time while their pain tolerance was lower, especially for the EP-born males. While similar HRQoL and health complaints were present in late adolescence, healthy EP-born subjects deteriorated towards early adulthood compared to their TB controls concerning psychological and psychosocial health.

7. Discussion

A holistic definition of health motivated this dissertation work, one that goes beyond a simple medical view to include well-being expressed in an individual's abilities or strength in the presence of disease. This perspective originated from an intention to move beyond use of traditional measures of morbidity after EP birth as an organizing framework — of which there is already a considerable body of knowledge — to measures that use subjective reports of health and well-being from the perspective of parents and the preterm-born children themselves to better understand how preterm birth affects holistically defined health.

The overall aim of this dissertation work was to investigate how EP birth affects health and well-being throughout childhood and early adulthood. We compared the developmental trajectories of HRQoL, emotional and behavioural patterns, and perception of and responses to pain of preterm-born subjects to those of matched control subjects born at term. Following two cohorts of EP-born children with approximately an 8-year birth difference at two chronological measurement points permitted us to gain new insight into development through critical phases in early life, i.e., puberty and transition to young adulthood. Long-term follow-up studies into adulthood are challenging because of the expanded assessment time frame and the risk of increased attrition. To our knowledge, few studies have successfully accomplished such an ambitious task. The results that emerged from this dissertation provide important new ideas to future focus of research for better understanding of health and well-being issues of EP-born children as they progress through early life.

In the following I will first discuss methodological issues followed by a general discussion of the results. The results were extensively discussed in Paper I to IV, and in this thesis work I will apply a more overall perspective.

7.1 Methodological considerations

7.1.1 Instrument-related limitations

The CHQ is one of the few generic measures that were developed for children at the time of the first follow-up done for this thesis work in 2001. It demonstrated good psychometric properties in different populations of children and discriminated between clinical samples of children and general samples, and it is able to detect clinical changes¹⁸⁵⁻¹⁸⁷. However, there was no experience using the CHQ in preterm-born children at that time. Later, we learned that it was sensitive for detecting changes related to preterm birth when compared to subjects born at term^{127,128}. The responsiveness of this instrument in this population was unknown, but we were able to detect changes across puberty in the youngest cohort. Therefore, we assumed that the CHQ had good responsiveness. However, we did not perform formal tests for sensitivity and responsiveness. One may question whether sensitivity was equal for all the scales, since there were signs of ceiling effects for the physical health scales of functioning and role limitations, especially for the responses of TB children. This has been reported in general populations, as well as in some clinical samples studied by Landgraf et al. (1999)¹⁸⁵. If ceiling effects were indeed present, this limits the possibility of detecting improvements.

SF-36 is a frequently used generic instrument with good psychometric properties across a variety of populations^{189,190,212,213}, and it captures the same health domains as the CHQ. It is considered to be the adult counterpart of the CHQ⁸¹. Therefore, it was a reasonable choice of tool for measuring HRQoL into adulthood. Since CHQ and SF-36 did not have the same construction, direct comparison of developmental trajectories was not possible. Several studies of EP-born individuals have gradually begun using this instrument.

Both the CHQ parent form and the SF-36 may be analyzed factorially and reduced to two summary scores comprising the psychosocial and physical component. In the first paper, we did report on these summary measures, but they were not used in later publications. We wanted to reflect more precise levels of well-being and functioning

within the different domains of health; therefore, we omitted the summary measures in this dissertation. Also, the underlying assumptions for the construction and accuracy of these summary measures have been questioned^{214,215}, and for the CHQ, use of the full range of scales is recommended²¹⁵.

The ASEBA instruments are extensively used in a range of clinical and general populations, showing good psychometric properties^{84,87,88}. They have frequently been used with preterm-born populations. They cover different aspects of emotional and behavioural problems. Often, they are presented as norm-based scores, but within the research context, raw scores are recommended⁸⁴. We used raw scores in this dissertation work.

7.1.2 Conceptual considerations

As pointed out in the Theoretical framework section (section 2.2) of this dissertation, confusion persists around the concepts being used within HRQoL research, and the notion that HRQoL, quality of life, and health status may be used interchangeably. We do agree that quality of life and HRQoL are distinct constructs, but we do not agree with the idea that HRQoL can be replaced with health status. Health status is more objective, but by including a qualitative dimension such as personal judgement of one's health, another perspective is added, which can be understood as HRQoL⁸¹. It is therefore questionable whether simply replacing HRQoL with health status, as proposed by Moons (2004)⁶⁶, will remove ambiguity. It seems more reasonable that researchers are clear about what have been measured in their studies and describe their results clearly.

What has then been measured in the present work? We claim to have measured HRQoL with CHQ and SF-36. Even though these measurements were developed to measure health status, they later were referred to as HRQoL measures^{71,77,212,216-218}. They measure domains that overlap with what is commonly understood as HRQoL, also in children^{71,81}. The way HRQoL measures are composed with a focus on well-being or functioning and limitations — the latter phrased as '*ill-being*' — is important for outcomes^{56,219}. Some measures seem to appraise well-being more than

others. Perhaps one simply has to acknowledge that measures of HRQoL comprise the presence of disease and that a personal evaluation by the subject gives value to how this matters in life. This is expressed within physical, mental, and social well-being, which corresponds to WHO's definition of health.

7.1.3 General limitations

Statistics

Generally, 5 to 10 points on a 0-100 scale may be considered to be a clinically important change for HRQoL data^{67,185}. However, one may question whether this is valid for every level of the scale or whether there is a critical value? There is no consensus answer to this question. The data may be reported as proportions according to a cut-off point⁶⁷. We chose to present differences in group means based on the manual of Landgraf et.al.¹⁸⁵. Concerning the ASEBA measurements, it is common to report critical values related to percentiles to indicate borderline or clinical cut-off points to differentiate between children²²⁰. For the measurements done for this thesis work, we reported results as mean differences.

Although the individual observations were skewed, we used parametric statistics, since there are no simple methods for analyzing correlated data non-parametrically. However in Paper I, we used both paired parametric and non-parametric analyses, and similar results were obtained.

A major limitation of our studies was the relatively small sample size. The main risk with small sample sizes is not being able to detect true differences between the groups, leading to type II errors. Or, if performing many analyses, there may be an increased chance of finding significant differences just by chance, leading to type I errors. Subsequently, wrong conclusions may be drawn.

As stated, no power calculation *a priori* was made for the HRQoL studies. The sample size was already given based on the power calculation for lung function studies done with the same populations. In general, post-hoc power calculations are not recommended and are regarded to be of little value⁶⁷. Calculating sample sizes in

HRQoL research is also not straightforward, since these measures usually consist of many possible outcomes, like the CHQ and SF-36. One may, however, use the sum scores for power calculation. As pointed out in Paper I, we did a post-hoc power calculation on the psychosocial sum score. Based on the obtained results from CHQ-PF50, we calculated an acceptable power of 80% to detect group differences between preterm and TB subjects of approximately 5.5 points on this summary score, provided that the level of significance was set at 0.05. According to the creator of the CHQ-PF50, when comparing a group mean to a fixed norm, a sample size of 69 or 18 is usually necessary to detect a 5- or 10-point difference, respectively, with 80% power at 0.05 significance level ¹⁸⁵.

By stratifying the data according to gender in Paper III, the size of the groups and thus the statistical power was reduced. The influence of gender on health issues, especially during puberty, is well known and has been documented in general populations for HRQoL and behaviour problems ^{79,86}. However, little is known about the gender-specific trajectories of EP-born children. Therefore, we aimed to explore this further, knowing that we could produce only suggestions for possible tracks not necessarily representative of other groups of EP-born children. The reviewers of the published paper pointed out the problem of limited power and designated the data to be pilot data, which we agreed to. Therefore, we considered the data to be only hypothesis generating. This may be a reasonable consideration given the limited knowledge, which implies that this issue requires further research in larger populations. Hypothesis-generating studies are common within epidemiology ²²¹.

Overall, we have specified results with 95% CIs for the purpose of presenting reliability of the estimates. This demonstrates the uncertainties of the results more explicit compared to what only a p-value can provide. Furthermore, a non-significant result may not indicate no effect only because the null-hypothesis cannot be rejected. Despite the limitations, we have been able to detect consistent differences between the group born EP and the group born at term, indicating that the sizes of the difference between the two were substantial and of clinical significance. We believe that the results are reliable, because they demonstrate consistency across findings.

There was a large variability within the measures, especially for the EP-born subjects, indicating that there is uncertainty in the true values for the target population; more specifically, some individuals do well, while others suffer more.

The low attrition rate in this dissertation work (Figure 2) strengthened the results. High rates of participation reduce the risk for selection bias and also increase representativeness. The follow-up rate in comparable studies that report on similar health outcomes as the present ranged from approximately 57% to 97%^{124,125,127-129,132,135,139,140,143}. In the present study, there were few subjects who did not participate in the second follow-up, and these were not particularly different from the participating subjects with respect to GA and BW (Table 4). All mothers of the non-participating subjects in the youngest birth cohort had an education attainment less than college/university.

The problem of attrition in follow-up studies in pre-school age seem to be related to sociodemographic characteristics, such as breakup of families, lower level of maternal education, and greater disability of the child^{222,223}. Whether these issues are also relevant in long-term follow-up studies into adulthood is partly unknown, but it is likely that the family situation plays a part in the attrition problem, as reflected in the present and in another report of EP-born young adults¹⁴⁵. The control group had a low attrition rate, which also secures the representativeness of the outcomes. Their response rate was high compared to response rates of similar studies of case-control subjects, ranging from around 40% to 90%^{132,135,139,140}.

The control group recruited for this dissertation work was recruited according to a strict system of the 'next-born-subjects' principle. This approach reduces the likelihood of selection bias, which is inherent to most other recruitment algorithms. Besides using this principle, similar studies have alternatively used voluntary classroom or peer-control recruitment principles, or have used no recruitment principle, deciding against using any subjects for a control group^{124,127,128,132,133,139,140,143}. We believe that our recruitment algorithm was good and that the control group was representative of average Norwegian children. In addition to the control groups, population norms could have been used; however, so far there are

no such norms available for the CHQ, and the existing norms for CBCL scales are not considered solid enough as national general norms²²⁴.

Other threats to generalizability of our results is the lack of consistency in defining the groups that were born preterm²²⁵. Both GA and BW are frequently used for classification. A uniform classification system was established in the beginning of the 2000s^{19,225,226}. Despite this, current research has used different inclusion limits for GA and BW, making comparison of results difficult. This applies for the present thesis work, which used inclusion criteria outside the established classification system of extremely low gestational age (ELGA) or BW. By including BW, there is a risk of including children small for GA, which could obscure outcomes as relating specifically to preterm children. There were, however, only a few subjects classified by BW in both birth cohorts (Table 5). Despite inconsistency in target populations, results are being compared across studies.

An irony of long-term research is that by the time the results are available, they may be outdated and no longer relevant to current populations, in this case those currently surviving EP birth^{225,227}. More specifically, survival rates have increased and treatment strategies have changed, possibly affecting outcomes. In the present study, the survival rates of the 1982-1985 and 1991-1992 birth cohorts were 63% and 74%, respectively. This reflects survival rates in those epochs and were even higher compared to relatively comparable groups for both cohorts^{124,127,128,131,228}. By including cohorts born pre- and post-surfactant usage, we were able to cover two eras considered important in affecting later outcomes²²⁹.

When comparing outcomes in HRQoL and behavioural issues in preterm-born children across nations, differences in populations, social systems, and culture will probably affect the results²²⁵. Correspondingly, when comparing HRQoL in ELBW adolescents from two European countries and Canada, there were significant differences among the three groups of subjects unaccounted for by BW, GA, or cerebral palsy²²⁸. By contrast, when comparing behavioural problems in ELBW school-aged children from four countries in Europe and North America, the problems

were similar in character, and the authors inferred that biological mechanisms contributed to these behavioural problems¹⁴⁸. In general, Norwegian parents seem to rate emotional and behavioural problems low compared to cross-cultural data, but quite large variation have been observed within the Nordic countries even though they are all “low-scoring countries”^{87,230}. In general, Norwegian adolescents also seem to rate emotional and behavioural problems low compared to cross-cultural data²³¹. This demonstrates one limiting issue in the generalizability of results across nations.

7.2 General discussion

HRQoL and emotional and behavioural difficulties

From a longitudinal perspective, we assessed the 1991-1992 cohort by parental reports at 10 and 18 years and the 1982-1985 cohort by self-reports at 17 and 24 years. Furthermore, we investigated whether behavioural and emotional difficulties — known to be a considerable problem in preterm-born children — predicted the development of HRQoL through adolescence. Occurrence of behavioural problems was confirmed in the 1991-1992 cohort, and we did find that early behavioural difficulties affected HRQoL assessed seven years later. Thus, behavioural issues seem to importantly affect HRQoL, especially within the psychosocial domains (Paper III). Recently, internalizing behaviour at 8 years has been shown to predict HRQoL in VLBW and very preterm-born children at adolescence, but not in TB controls¹²⁶. As we found this also in TB subjects, it might indicate that early behavioural problems affecting later HRQoL could be a general phenomenon.

This observed significance of emotional and behavioural problems on HRQoL is in line with the view that mental health problems have a negative effect on HRQoL, as documented in studies both with children and adults with ADHD and in studies of the general population^{71,232-237}. In children and adolescents with ADHD, the psychosocial components of HRQoL and parental and family impact are the most impaired

^{234,235,237}. For preterm-born young adults, depression is correlated with HRQoL ^{145,238}, and it predicts HRQoL in 23-year-old ELBW adults ¹⁴⁵.

We initially pointed to the family and parents' significance for development of behavioural control in EP-born children. Nurturing these children may be challenging, and this underscores why the functioning of the family and parental concern are special issues when addressing HRQoL in children ⁸¹. From the very beginning, preterm birth is a stressful event that poses a tremendous challenge for the whole family, one persisting through childhood and into adolescence ^{91,239}. This point was underscored by the parental and family strain these parents reported when their children were assessed in childhood, consistent with the few previous reports on this issue ^{127,128}. Despite improvement when assessed at 18 years of age, the challenge continued to have an impact on the parents emotionally (Paper I and III). Parents are faced with the uncertainty of whether their child will survive, medical complications, and possible long-term effects on their child's health ²⁴⁰. Increased parental stress and impaired maternal mental health coupled with depression and anxiety have been reported in families of preterm-born children, especially occurring within the first years of the child's life ^{91,93,241}. This parental stress may persist and may contribute to the behavioural problems of these children ^{91,94,242,243}. Inherent in this situation is the important mother-infant interaction, which may be affected negatively and increase the risk for insecure attachment ^{242,244}. This has been demonstrated in late adolescence ²⁴⁴.

As reported in Paper I, we found robust significance of the role the child's health plays in parent and family functioning. One may speculate to the origin of these effects on the parent and the family. The increased parental stress may relate to their child's disposition, such as being more demanding, having difficulties with social-emotional and cognitive development, or to family factors and level of social support ^{91,240,243,245}. We did not collect any information on parental stress or mental health, so how these factors could have influenced the reduced parent-related HRQoL is uncertain. Also, we cannot determine how such factors might have influenced the child's health. Higher education attainment has been associated with better coping

strategies that lower stress, in mothers of both VLBW and TB children^{245,246}. In the present study, only maternal education was demonstrated to be possibly acting as a proxy for socioeconomic status, but it did not seem to contribute to the observed differences in comparison to the TB children. We did have mothers with lower educational attainment in the EP group at both measurement points. The lack of an improved educational attainment for mothers of EP-born children may be a sequelae to EP birth, an idea advanced in a previous report²⁴⁵.

There has been a shift in how parents are involved in the care of their child in the NICU over the past approximately 15 years. At the time of birth of the present two cohorts, parents were scarcely involved in the care of their child in the NICU. The nature of their involvement was more in the realm of visiting for some hours during the day. There has been more involvement of parents for children born in the 1990s compared to the 1980s. This is in contrast to present day NICUs around the world, especially in Scandinavian countries, where they tend to be more family centred and have implemented the Newborn Individualized Developmental Care and Assessment Programme (NIDCAP care)²⁴⁷.

Subsequently, educating caregivers to attune themselves to the neonate's behavioural responses has optimized care. The nature of care has also shifted so that parents are now the primary caregivers. Other improvements include organizing a facilitating environment²⁴⁸ and applying skin-to-skin care more regularly and frequently²⁴⁹. Early intervention programmes developed for increasing parents' sensitivity towards their child's expressions and enhancing attachment has produced some evidence for a way to reduce stress in Norwegian parents of preterm-born children up to 9 years of age²⁵⁰. These may also have a positive effect on child behaviour^{242,251,252}, although not consistently in more moderately preterm born children where assessment age may be involved^{253,254}. One meta-analysis on stress in parents of preterm-born children from birth up to 12 years over the course of 20 years from 1980 to 2000 reported decreased parental stress with time²⁴⁰. One explanation put forward was that including parents in the care of their child in the NICU has the potential to reduce parental stress²⁴⁰ and furthermore, improve parent-child interactions.

We discussed in Paper I reports of perceived “professional” inadequacy of the parents when caring for their child during childhood, indicating that they had not received the support they needed. This was the case, even though two-thirds of the children actually received academic or psychological support during this period. The latter suggests that there are other concerns that are not addressed, or not so easily captured in assessments. These concerns may not necessarily be related to the child alone, but to the parents and to the family as a whole. At the time when the two cohorts were discharged from hospital, there were no guidelines for follow-up, although neonates weighing less than 1500 grams were followed by the specialist health service during their first years. One may question if regular follow-up programs accommodate the need of the family and child when discharged from hospital.

Even though the discharge from hospital is a long-yearning event, the transition to the home environment may be challenging, one in which the entire responsibility for the health and development of the infant lays with the parents. In addition to the above-mentioned early intervention programmes performed in the NICU setting, home interventions have shown to be promising²⁴². One such intervention employing regular home visits by a team of psychologists and physiotherapists over the first year demonstrated encouraging results, showing better parental mental health and fewer behavioural problems in the children when assessed at both two and four years of age^{255,256}.

Parental versus child report

We believe that it is especially important to obtain an assessment of HRQoL that the EP-born subjects provide themselves, not just one judged by the parents. Of course, this is provided that the questionnaires are suitable for children to complete. Although the child form of the CHQ was developed for use by children from 10 years and older, it is questionable whether this age limit is appropriate for every child. The fact that the child CHQ form has 87 items to be completed and that the items have several response categories, it seems that this may be a challenge for some children. We have not seen it completed by EP-born children at that age. Other studies that have

assessed HRQoL during childhood typically employ parental reports of their children¹¹³, with apparently only one exception¹⁴¹. So, our procedures are consistent with these earlier reports. We had to rely on the parents' judgements of their child when assessing developmental trajectories through puberty in the 1991-1992 birth cohort.

The present finding that parents report poorer HRQoL for their EP-born children and more emotional and behavioural difficulties (Papers I and III and Table 6) seems reliable compared to previous research^{10,11,149,257}. At 18 years, adolescents supplemented these findings with self-reports (Paper III), and the subjects in the 1982-1985 birth cohort self-reported their development of HRQoL from 17 to 24 years of age (Paper IV). When the EP-born children reported on health and well-being as adolescents, they perceived their situation relatively similarly to their TB peers, consistent with what most others have reported concerning physical and emotional well-being¹²⁸⁻¹³⁰ and social well-being^{131,132}. However, some have reported poorer physical functioning^{131,132} and poorer emotional well-being¹³¹. The patterns of emotional and behavioural problems were perceived relatively similar to TB peers as well; consistent to other reports^{150,154,159,160}, with one exception¹⁵². Even though no comparisons were made between the children's self-reports and the parents' reports, the children's seemed to be relatively coherent at the 18 years of age assessment.

When it comes to a parent assessing a child's HRQoL and behaviour, there are certain limitations. Parents must be seen as important contributors to the understanding of their child's HRQoL and behaviour, as long as the child has not reached adulthood, and they are considered to be reliable proxy raters^{81,258}. It is not surprising that parents know their child well and may provide valuable and reliable insight into their child's well-being and functioning. However, factors discussed earlier regarding caregiving, the quality and burden of it, parents' own mental health and well-being, and factors related to social and economic status may influence the parents' view of the child's HRQoL^{80,80,81,259,260}. In general, parents and children make different judgements about HRQoL and behaviour, so low correlations are to be expected^{80,261}, which was also confirmed in a general Norwegian population study

²⁶². This seems especially true for judgements made in areas related to psychosocial factors rather than physical ones ^{80,260}. One assumes that parents perceive illness in their child to have more negative consequences than does the child ⁸⁰. However, better agreement has been obtained between parents and chronically ill children compared to parents and healthy children ⁸⁰.

The longitudinal perspective

The tendency for EP-born children to perceive their HRQoL and behaviour in adolescence and in young adulthood as being comparable to TB peers is reassuring ²⁶³. The shift to self-report during adolescence gives the impression that preterm birth no longer affects their health specifically by the time they reach this stage. Self-reports from different age cohorts and more moderate preterm-born subjects support this impression ²⁶⁴⁻²⁶⁷. However, one has to acknowledge the possibility that a change might occur in intra-individual standards and adaptation across ages, which may affect self-perceived measures of health as well as parent reports ^{67,268}. One may speculate if this possible change reflects truth or, alternatively, acceptance and adjustment to the current situation. Another possibility is that this shift represents denial of problems and an overriding desire to be similar to peers and to present themselves favourably. This issue has been discussed by Saigal ^{142,263}. Strangely, higher 'lie scores' (tendency to give false answers) have been observed in adolescents who are born EP compared to TB ²⁶⁹; this could threaten the reliability of self-reports. Nevertheless, the parents in this thesis work reported improved HRQoL and behaviour when assessed in their children at 18 years old, supporting the impression self-reported by the adolescents. This positive development according to their parents view is contrary to the limited existing knowledge on HRQoL from self-reports ^{124,143,145}. However, it is difficult to compare results as differences in measures, inclusion criteria and ages when assessed were applied. These limitations apply to the reports on behavioural patterns as well.

Even disabled EP-born subjects seem to have relatively good HRQoL, despite physical limitations. Their situation may be more easily acknowledged, and required

arrangements through habilitation programmes may have been established. This is in contrast to the healthier EP-born subjects who may have more subtle problems that may not be so easily recognized. This could make them potentially more susceptible as they emerge out of adolescence into adulthood. In the present study, parents of EP-born children reported persistent poorer competence, which was also reported by the EP-born females; this highlights a possible vulnerability (Paper III). This vulnerability may be a manifestation of what has been reported as educational underachievement, less physical capacity, more emotional problems, and social insecurity⁵⁶. In this thesis work it possibly appears as fewer perceived coping strategies. As long as children are living at home under the protection of their parents, they manage to keep up with their peers. At the beginning of a more independent and self-supportive life — marked by completion of their formal education, securing a job, and possibly getting married and having children — this vulnerability may become more apparent.

In modern society, a longer period of approximately 25 years now seems to be required before ‘real’ adulthood is reached and a more settled life structure is achieved²⁷⁰. This would mean that in EP-born children, adult perception of HRQoL does not emerge until this age (i.e., ~25 years old). This may be reflected in that both the EP-born subjects in the 1991-1992 cohort and the 1982-1985 cohort reported a relatively similar HRQoL level at around 18 years of age, which was also similar to their TB peers. When the 1982-1985 cohort reached 24 years of age, their psychosocial HRQoL was impaired and their psychological health complaints increased compared to TB peers. At this age, the EP-born children displayed educational underachievement, which was indicated in the youngest EP-born subjects as well. Even at 18 years old, there was some indication from the parent reports of the 1991-1992 cohort that there remained some noteworthy differences that might be important for future well-being and functioning.

The literature on HRQoL of EP-born subjects at adult age is sparse at this point, but there are some studies supporting our finding of poorer self-perceived mental HRQoL, all in older generations of preterm born^{135,136,140}. Furthermore, there are

several reports of increased risk of psychiatric morbidity among adolescents and young adults born preterm^{147,170,271-274}. Despite this, the prevailing impression is that very preterm-born infants have better functioning in adulthood than expected, although still with some concerns for future health and functioning⁵⁶. The younger generations of subjects have not yet reached adulthood, so we do not know yet if better neonatal intensive care and follow-up in their generation will cause fewer sequelae in the long term, or result in more vulnerable infants due to increased survival. The impression given by the parents from the 1991-1992 cohort is promising, both in that the EP-born boys improved their health and well-being substantially, and in that the EP-born girls were less affected. The other, and more worrying, impression emerging from the study of the 1982-1985 cohort of the EP-born children assessed in young adulthood, is that EP birth is a persistent challenge for their well-being and functioning, especially with regard to psychosocial HRQoL. This appears particularly to be true for the healthier EP-born subjects.

Pain

EP-born neonates are exposed to an extensive number of painful and stressful events during hospitalization, not necessarily all recognized and treated^{275,276}. However, there is some evidence of improved neonatal pain management over the decades^{277,278}. In the present study, the number of painful procedures ranged from 15 to 505, in addition to all the other countless, stressful events. This situation of early pain experience may have long-term consequences for pain perception^{109,279}. When assessing pain experience in adolescence, we did not find increased levels of pain symptoms in comparison or that pain interfered more with daily life in those born EP than at term. This is consistent with the few other reports of self-reported pain in EP born in adolescence^{153,174}. We did, however, observe that those born EP had lower pain tolerance which, to our knowledge, has not been specifically addressed by others. However, as discussed in Paper II, there are some conflicting findings in how early pain exposures might affect later sensitivity to pain, in that both hypo- and hypersensitivity have been reported^{175,177,279}. In one paper assessing pain sensitivity by evaluating tenderness points and tenderness threshold, that were respectively

increased and lowered in the preterm-born adolescents compared to TB peers, it was anticipated an increased risk for developing pain syndromes later in life¹⁷⁴. A review article suggest that fibromyalgia, which is characterized by increased pain sensitivity along with several affective co-morbidities, may partially be explained by high exposure to painful experiences early in life²⁷⁹. Our findings do not indicate this, but at 18 years of age it may be too early to address conditions related to fibromyalgia. A Norwegian population study of 13-19 year-old subjects, the Young-Hunt study, found no association between preterm birth or low BW and chronic pain²⁸⁰, which is consistent with our findings.

To be noticed, also in the self-reported HRQoL bodily pain scale, we found similar results for the EP-born and TB children in adolescence, which was in line with the parent reports. One might expect that with such a subjective phenomenon as pain, the parents' perceived pain of their child would likely be different from what the child reports, but in the present study, we found that they actually coincided relatively well. Our results correspond well with what others have reported^{126-129,132}.

One has to consider that the pain experiment, with which we directly assessed responses to physical pain, is a more objective way to measure pain perception, whereas self-report of pain is a subjective way. The results obtained from these two different ways of measuring pain perception did not correspond, even though both pain tolerance and pain intensity ratings are not specifically biological or sensory aspects¹⁹⁵. They may be seen as results of different interacting factors, as demonstrated by the biopsychosocial model of pain, highlighted in the introduction⁹⁹. The appraisal of a pain event may be a result of sensory stimuli, cognitive evaluation, and motivational and emotional aspects⁹⁹. Such factors may result in a difference in tolerating pain and the awareness the pain elicits²⁸¹. The CPT experiment mimics well clinical pain and may represent a stressful event. The EP-born children may be more sensitive to stress in adolescence, as pointed out earlier in this dissertation and also discussed by Grunau¹⁰⁹; this may be manifest in clinical settings. Even though the EP-born and TB children accepted without hesitation to participate in the pain experiment as adolescents, they could very well have been challenged differently.

As a group, the EP-born children perceived pain intensity during the CPT experiment similarly as the TB peers, with both groups showing high values on the numeric rating scale. Despite this similar perception of intensity in adolescence, the EP-born children demonstrated less tolerance. This was especially true for EP-born boys, which is unexpected for boys in general ¹⁹⁶ (Paper II). One may speculate how psychological processes contributed to pain perception during the CPT experiment. It could be that the EP-born children felt less confident in managing stressful situations, as manifested by a lower GSE, which in turn was manifested by a lower tolerance to pain. GSE is a psychological factor that is known to increase tolerance to pain ²⁸¹.

As noted earlier, GSE develops by receiving input from different sources and is also learned within the family. Moreover, social learning may influence children's experience of pain. Parents of EP-born children may interact less functionally towards the child due to different factors inherent to the child and the parent ^{91,282}. The mothers of EP-born children have been described to be more solicitous towards their child's pain and may even cultivate impaired functional behaviour towards pain ¹⁷⁸. We also found that high maternal educational attainment was associated with increased pain tolerance in all subjects, but mothers of EP-born children had lower educational attainment. When controlling for these possible interacting factors, there was still a difference in pain tolerance, which might be related to altered pain sensitivity.

7.3 Factors associated with outcomes

The factor of gender was of central importance in our results, as demonstrated by the finding that school age EP-born boys differed from the TB boys in nearly all HRQoL domains, especially in the psychosocial domains of HRQoL and in the parental domains. In the youngest cohort, there were more boys than girls with minor impairments, which could have contributed to this main effect. The effect of male gender on parental emotional impact was consistent with results from another Norwegian study of VLBW children assessed at 14 years of age ¹²⁸. Results from the follow-up to 18 years in our study demonstrated that the EP-born males improved

substantially, approaching scores of their TB peers. This was not the case for the EP-born females, who differed less from the TB girls at 10 years of age. The effect of gender was discussed in Papers I, II, and III.

We did not exclude data of any of the children with minor disabilities in the analyses, except in a subanalysis of pain tolerance; this, however, did not change the results (Paper II). Usually, subjects with major impairments are excluded or treated separately, which we did in the analysis of the 1982-1985 cohort (Paper IV). When we accounted for ADHD or mild mental retardation, as was done for Paper III, this did not change the results. The disabilities factor was not controlled for in Paper I. However, learning and/or attention problems were controlled, the latter being a major component of ADHD. Learning and/or attention problems did influence HRQoL, and this was especially evident for EP-born children in some of the HRQoL scales (Paper I). The way impairment interferes with HRQoL is not consistent across studies, except for poorer physical functioning in subjects with more severe disabilities. Impairment accounted for poorer HRQoL in school age up to adolescence^{122,123,126}, but was of little significance at older ages^{132,146,263}. This may be understood partly in terms of parent reports versus self-reports, as discussed earlier.

With regard to maternal education, we did not consistently include this factor in the regression models. Mothers of EP-born children in the youngest cohort clearly had lower educational attainment than mothers of the TB children, but this was not the case for the fathers. Therefore, the possible social inequality might be compensated for. In Paper I, we did examine whether the results were changed by including maternal education in the regression model; however, they remained virtually unchanged. In the follow-up (Paper III), maternal education was controlled for in the regression models of the parent reports and self-reports; this did not change the results. The significance of this factor may depend on outcome, and it has to be considered how much it might reflect family socioeconomic status^{8,283}. In HRQoL studies, little is known about the contribution of this factor, but the few studies that have included maternal educational attainment in the analysis, the results are inconsistent for self-perceived health in VLBW young adults^{134,143,146}.

GSE

GSE was lower in the EP-born children assessed as adolescents. When controlling for this factor in the different regression models in the 1991-1992 cohort at the 18-year assessment, it did not appreciably change the results. However, we did notice that in adolescence it influenced self-reported HRQoL, behaviour, and pain tolerance for both EP-born and TB children.

This aspect has been investigated very little in EP-born children. To our knowledge, only one study of HRQoL assessed at 19 years of age has included GSE as a possible influencing factor on HRQoL and it did not find a significant contribution¹⁴³. GSE is one psychological factor that can be modified and strengthened, and it may be important for HRQoL²¹⁰. This has been demonstrated in a general population of school children, where GSE was considered to be a health-promotion factor^{284,285}. GSE must not be confused with self-esteem, which refers to a different entity¹¹⁸. However in the present study, self-esteem was perceived to be relatively similar in EP-born and TB children when assessed in adolescence.

Neonatal factors

The impact of neonatal variables may be expected to be less significant when children grow older and when long-term outcomes, such as in the present, are examined¹⁴³. In HRQoL studies, neonatal factors have been scarcely investigated, although it appears more often in studies of emotional and behavioural problems. BW and GA are variables expected to affect these outcomes. Association of BW ratio to CHQ scores was evaluated in univariate analyses in Paper I and was found to be insignificant.

In the present study, the distribution of BW and GA, as defined by the inclusion criteria, was relatively narrow, and the sample size was limited. Therefore, the potential of these two variables to influence outcome was reduced. However, the fact that the preterm subjects differed from the control subjects in HRQoL and behaviour, supports the notion that GA and BW have an effect. One Swedish study found that

physical HRQoL is associated with both GA and BW in VLBW children assessed in young adulthood¹³⁴. Lower BW has been reported to be associated with inattention and psychiatric diagnoses in adolescents, and GA to psychiatric diagnoses in VLBW children tested as adolescents²⁸⁶. This is supported by others, who conclude that BW predicts behaviour problems^{163,287}. The number of SGA in the youngest birth cohort in this dissertation work did not influence HRQoL or behaviour. Another Norwegian study has reported similar HRQoL scores at adolescence in terms of SGA and control adolescents¹²⁸, but at young adulthood the psychosocial HRQoL was inferior in the SGA adults compared to TB peers¹³⁵.

When investigating other different neonatal factors in univariate models, we found that those who had received neonatal steroid treatment for BPD performed more poorly on the role social functioning scale due to emotional and behavioural problems at 10 years of age. However, this was not found at 18 years of age. The above-mentioned Swedish study reported an association of mechanical ventilation, BPD, and IVH on physical HRQoL¹³⁴. We found mechanical ventilation to be related to social, thought, and attention problems (Paper III). One study has reported increased behavioural problems in school-aged BPD children¹⁴⁴. Recently, it was reported that neonatal-administered morphine and procedural pain predict internalizing behaviour in childhood¹⁶⁵.

In Paper II, we discussed the influence of neonatal factors on pain tolerance, based on other research reports^{105,288}. Our findings were contrary to what we expected, showing a tendency of *increased* tolerance with increased exposure to morphine, painful events, and more mechanical ventilation. However, the associations seemed more pronounced for a low number of exposures, raising the question of a possible critical developmental period being present¹¹⁰. Furthermore, there is extensive collinearity among these variables that precludes the understanding of these issues within the constraints of the present study.

7.4 Clinical implications

This thesis contributes to the knowledge of how EP birth affects health and well-being for the child and the family in the long term. This new information is important for both professionals and for those affected directly, the children and families. Our findings underscore the importance of obtaining subjective information from both the perspective of the parent and the EP-born subjects, and to follow them through critical developmental phases in life. Inherent in this kind of long-term research is the uncertainty of generalizability and relevance for newer generations of EP-born survivors. In the future, one has to rely on current research.

Despite limitations, one novel finding of this dissertation work was how being an EP-born male might possibly influence development of HRQoL and behaviour, and affect pain tolerance. Furthermore, our results suggest that early identification of emotional and behavioural difficulties may be important, as they may contribute to poorer health and well-being in the long term. Early identification could then lead to early intervention. In addition, it is worth noting that GSE may possibly influence health and well-being.

The findings indicate that it is important to address not only the child but also the whole family, which is so important for the development of the child. This knowledge may be valuable not only to the specialist health-care service responsible for the follow-up programme after EP birth, but also to professionals in the municipal health-care and educational services, as well as to NICU staff. The nurturing of these children starts in the NICU; hence, it seems reasonable to support the commencement of family-centred care practice in NICUs, although the benefits of specifics of such practices need to be explored. Despite the fact that many NICUs do not have the space for parents to stay together with their child 24 hours a day, they may find good solutions for including parents in the care of the neonates. Also to be considered is whether the NICU staff is knowledgeable of available early intervention programmes and is trained for implementing them. If educating and sensitizing parents is a key component in the care, the staff also has to be trained in these skills, and the

necessary resources have to be made available. Along with this, is the importance of improving neonatal pain management and reducing inappropriate stressful and painful stimuli for these vulnerable children^{107,288}.

Even though we tacitly concluded that everyday pain might not be a problem in this particularly vulnerable group of children, we were less certain about the significance of their impaired tolerance to pain. However, it seems important that professionals who face EP-born children in different clinical situations be aware of their early pain experience, which might influence how they approach the management of current pain events in this kind of patients.

7.5 Future research

Longitudinal research is warranted for addressing health and well-being issues, both for existing cohorts, but also for newer cohorts born in the era of new approaches to neonatal intensive care and treatment. Preferably, these cohorts should be studied longitudinally well into adult life. Adequate sample sizes and low attrition rates must be obtained if at all possible.

The gender issue requires further research and in larger populations of EP-born subjects to determine how gender might affect development. Furthermore, there is a great need for more knowledge on and understanding about which domains are specifically important for health and well-being after EP birth and about early predictors of HRQoL. We need more research about the significance of emotional and behavioural problems for HRQoL, and also about how factors such as GSE may have the potential to improve health and well-being. There is a need also for more knowledge and understanding about how parents and family interact and influence HRQoL of the child, and how the child affects the parents so that they can provide sufficient and appropriate care and support.

It may be important to the research field to reach a conceptual consensus on HRQoL to know what has been measured and then to employ similar instruments to compare results across studies²⁸⁹. This leads to building solid evidence. A relatively new

HRQoL instrument for children has been developed, the KIDSCREEN^{290,291}, which can make it easier to obtain child reports.

Finally, intervention studies aimed at relieving parental stress and improving behaviour and cognitive skills of the child have been performed and warrant further investigation of their efficacy in the long term, especially their effect on HRQoL. Furthermore, it seems reasonable to continue to develop appropriate individualized and goal-directed interventions. Herein, it may be beneficial to include qualitative studies, which are now more or less completely absent²⁸⁹. It is important to go beyond data and numbers to better understand the story of the person and thus gain new insight. Mixed methods that incorporate both qualitative and quantitative measures may be useful in this regard.

8. Conclusions

At 10 years of age, children born EP in 1991-1992 without severe impairments were reported by their parents to have poorer HRQoL within several domains. Compared to TB children, they also had more emotional and behavioural difficulties and less competence. Psychosocial HRQoL and strain on family and parents were most strongly affected, while physical functioning was less impaired. These differences were mainly explained by scores of the preterm-born boys, while the girls were less affected. The parents of the EP-born children reported that their 18-year-old adolescents improved on HRQoL and had fewer emotional and behavioural difficulties than at 10 years when compared to their TB peers. This was especially evident for EP-born males. Emotional and behavioural difficulties at 10 years of age predicted poorer development of HRQoL for both EP and TB subjects. The EP-born children themselves perceived both their HRQoL and behaviour at adolescence to be relatively similar to their TB peers. GSE was associated with better HRQoL and behaviour.

At 18 years of age, children born EP in 1991-1992 demonstrated reduced pain tolerance to having their hand submerged in ice water compared to TB adolescents, an effect that was partly explained by the disproportionate performance of EP-born boys. However, both EP-born and TB children perceived pain intensity similarly and had similar level of health complaints at 18 years of age. GSE and high maternal educational attainment influenced pain tolerance positively for all subjects.

Subjects born EP in 1982-1985 reported similar HRQoL and health complaints at 17 years of age, except for EP-born children with severe impairment, who reported impaired physical functioning. At 24 years of age the healthy EP-born children reported lower psychosocial HRQoL compared to their TB peers. Furthermore, they also reported more psychological health complaints compared to measures obtained at 17 years and compared to their TB peers at 24 years of age.

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