Exercise Capacity After Extremely Preterm Birth

Development from childhood to adulthood

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All parts of the body which have a function,
if used in moderation and exercised in labors in which each is accustomed,
become thereby healthy, well-developed and age more slowly,
but if unused and left idle they become liable to disease,
defective in growth, and age quickly.

In principle; there is less risk in activity than in continued inactivity.

Hippocrates (460-375 B.C.)

CONTENT

1. ABBREVIATIONS

AGA	Accurate for gestational age
AT	Anaerobic Threshold
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
BPD	Broncho Pulmonary Dysplasia
BW	Birth weight
CI	Confidence Interval
CLE-test	Continuous Laryngoscopy during Exercise -test
COPD	Chronic obstructive lung disease
DOHaD	Developmental origins of health and disease
EILO	Exercise Induced Laryngeal Obstruction
ELBW	Extremely low birth weight
EP	Extremely Preterm
FEF_{25-75}	Forced Expiratory flow at 25-75% of FVC expired
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Volume Capacity
GA	Gestational age
Hb	Hemoglobin
HR	Heart rate
LLN	Lower limits of normal
LMP	Last menstrual period
LVCP	Left vocal cord paralysis
NICU	Neonatal intensive care unit
PA	Physical activity
PDA	Patent ductus arteriosus
$Peak\dot{V}O_2$	Peak oxygen consumption
RDS	Respiratory distress syndrome
SD	Standard deviation
SGA	Small for gestational age
SV	Stroke volume
VE_{max}	Maximum minute ventilation ($mL \cdot kg^{-1} \cdot min^{-1}$)
VLBW	Very low birth weight

2. SCIENTIFIC ENVIRONMENT

This thesis is part of the PhD program at the Department of Clinical Science at the University of Bergen, and the research was performed within the frames of "*Research group for paediatric follow-up studies*". The ideas and research questions were conceived at the Department of Pediatrics at Haukeland University Hospital, where the clinical examinations were performed.

The major funding institution was Western Norway Regional Health Authority, Haukeland University Hospital and the University of Bergen, Norway.

The thesis is based on two regional cohorts of extremely preterm-born children established in 2001 by my main supervisor, pediatrician and professor Thomas Halvorsen. I was invited to join this research group in 2008 to conduct the second follow-up.

My co-supervisors has been pediatrician and Professor Trond Markestad, who is also the head of the "*Research group for paediatric follow-up studies*", and PhD. Scient. Ola Røksund who also performed the lung function and exercise tests in the study.

Statistical analyses were carried out in collaboration with biostatistician Prof Geir Egil Eide, Centre for Clinical Research, Haukeland University Hospital, Bergen, and Department of Global Public Health and Primary Care, Research Group on Lifestyle Epidemiology, University of Bergen, Norway.

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4. ABSTRACT

Background: Extremely preterm (EP) birth is associated with a series of adverse health outcomes, some of which may be alleviated by improved physical fitness. Subjects born EP are reportedly less physically active than term-born peers, measures of exercise capacity are poorly described and longitudinal changes are unknown.

Aims: To investigate associations between EP birth and exercise capacity in later life.

Methods: Two area-based cohorts born at gestational age ≤ 28 weeks or with birth weight ≤ 1000 grams in 1991-1992 and in 1982–1985 were examined at 10 and 18 and at 18 and 25 years of age together with matched term-born controls using an identical maximal cardio-pulmonary treadmill exercise-test and validated questionnaires. The main outcome variables were maximal oxygen consumption and the distance completed at the exercise test.

Main Results: Measures of exercise capacity was decreased by approximately 10% in EP-born compared to matched term-born control groups; however, with mean values within levels considered normal. Differences between EP-born and term-born controls were largely explained by differences between the males, but this apparent gender difference did not reach statistical significance when tested with interaction terms. Changes in exercise capacity from 10 to 18 and from 18 to 25 years of age did not differ from what was observed for term-born controls. A neonatal history of surgical closure of a patent ductus arteriosus was a risk factor for left-sided laryngeal paralysis with an associated increased risk of respiratory symptoms and airway obstruction, but exercise capacity was not reduced. A neonatal history of bronchopulmonary dysplasia was unrelated to current measures of exercise capacity, and we were unable to disentangle strong associations between neonatal factors and later exercise capacity. Current FEV_1 was unrelated to measures of exercise capacity. At 10 years of age, no associations were observed between reported physical activity and peak$\dot{V}O_2$, whereas at older ages these two variables were significantly and positively associated in both the EP-born and term-born groups in both participating birth-cohorts.

Conclusion: Mean exercise capacity was approximately 10% poorer in EP-born than term-born participants; however, values were basically normal and unrelated to most neonatal factors and to current FEV_1. Changes from mid childhood to adulthood were

parallel in the EP-and term-born groups. A positive association between exercise capacity and self-reported physical activity developed through puberty in both the EP and term-born groups, suggesting similar trainability.

5. LIST OF PAPERS

1. **Aerobic capacity and exercise performance in young people born extremely preterm.**
   Clemm H, Røksund O, Thorsen E, Markestad T, Halvorsen T.
   Pediatrics. 2012 Jan;129(1):e97-e105.

2. **Exercise capacity after extremely preterm birth: development from adolescence to adulthood.**
   Clemm HH, Vollsæter M, Røksund OD, Eide GE, Markestad T, Halvorsen T.
   Annals of the American Thoracic Society. 2014 May;11(4):537-45

3. **Exercise capacity after extremely preterm birth: Changes from childhood to adulthood.**
   Clemm HH, Vollsæter M, Røksund OD, Markestad T, Halvorsen T.
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6. GENERAL INTRODUCTION

Survival after preterm birth has increased considerably over the last decades (1). The improved treatment options that have become available during this period have been to the benefit of all preterm-born individuals, but have particularly facilitated survival of the most immature infants (2). This scenario opens for long-term cohort effects that are difficult to predict; i.e. possibly improved outcomes for the "average preterm-born" but also a potential for worse outcomes due to the vulnerability of those infants who were born at the very limits of viability.

Play and sports are fundamental elements of a normal childhood, and also important for subsequent long-term development of body and mind. Individual involvement and success on this arena is influenced by a range of factors among which is the ability to endure physical activity, often referred to as the exercise capacity or the exercise performance of the child. It has been known since the days of Hippocrates that physical activity is necessary to maintain good health.

A stringent definition of exercise capacity is difficult to extract from the literature, but it can be expressed as the amount of physical exertion someone can sustain in a given activity, such as distance covered on a treadmill-test, or by the highest rate someone can consume oxygen (peak$\dot{V}O_2$) (3). In epidemiological research performed in the general population, peak$\dot{V}O_2$ is inversely related to risk factors for so-called life-style related diseases, such as cardiovascular disease and diabetes type 2 and also to mortality (4).

In preterm-born children and adolescents, one can envision several features that can potentially interfere with physical performance and exercise capacity, such as respiratory impairments due to airway obstruction or disturbed alveolar development, cardiovascular disease, neuromotor, sensory or cognitive deficiencies and behavioral shortcomings or abnormalities. Physical inactivity due to real or perceived limitations or weaknesses in these children may further incite negative circles with long-lasting negative effects.

Studies have shown that preterm-born children exercise less than their term-born peers. Additionally, there is an increasing concern that preterm birth by itself can be a risk factor for cardiovascular disease (5), hypertension (6), diabetes type 2 (7) and even early death (8); risks that potentially may be alleviated by better physical fitness. It is therefore important to increase our understanding of exercise habits and exercise capacity in preterm-born children, adolescents and adults.

Thus, the overall aim of this thesis was to study exercise capacity in preterm-born children, adolescents and young adults, mainly through measurements of peak$\dot{V}O_2$, emphasizing particularly longitudinal development. We also aimed to search for associations between exercise capacity and perinatal variables and exercise habits.

6.1 Extremely preterm-born individuals – our new fellow citizens

Birth represents the greatest physiological transformation encountered during a lifetime; a miracle happening every day, still with countless unanswered questions. To be *born preterm* implies that growth and fine-tuned development designed to take place in a sheltered and controlled intrauterine environment must occur within the frames of a neonatal intensive care unit (NICU).

During the past 3-4 decades, better understanding of the needs of preterm-born infants combined with major development of technology and medicinal remedies have led to vast improvements in their survival. Providing access to proper perinatal care, up to 80-90% of those born extremely preterm today survives (9, 10); figures that characterized the death-rates for this group in the 1970s. The full consequences of being born extremely preterm are yet to be understood, as the first pioneer subjects only recently have entered early adult life. The data obtained from the young preterm-born adults of today will by nature describe "*NICU graduates"* born in the 1980s who were treated quite differently from current NICU patients. Nevertheless, these outcomes provide the best estimates currently available for what to expect also for today's extremely immature survivors, until superseded by new data as the current generation NICU patients grow older.

6.1.1 Preterm birth

The World Health Organization (WHO) defined in 1948, preterm birth as birth before 37 weeks of completed gestation (11). The burden of preterm birth is substantial, and it is worldwide the second most common cause of death in children under 5 years (1). Approximately 15 million babies are born preterm every year, the proportions ranging from 5% of all newborn in European countries to 18% in some African countries. The majority of preterm births occurs in low-income countries. Nevertheless, USA is one of the ten countries with the highest preterm birth rates with 12% (12). As much as 1 million babies die each year due to preterm birth, most of them born in low-income countries.

Preterm birth is increasing in nearly all countries (13, 14). In a majority, no cause is identified; however, some of the risk factors are known and of maternal origin, like socioeconomic demographics, maternal smoking, poor nutritional status, systemic diseases, stress and genetic factors. Multiple pregnancies due to increased maternal age or infertility treatment, cervical insufficiency, uterine surgery and genital infections are also important risk factors (15-17). More use of ultrasound scanning may have led to higher rates of deliveries being classified as preterm, due to lower gestational age (GA) estimates than those set by the last menstrual period of the mother (18).

Table 1.	Gestational age, weeks	Birth weight, gram
Extremely preterm	< 28	
Extremely low birth weight (ELBW)		<1000
Very preterm	28- <32	
Very low birth weight (VLBW)		<1500
Late preterm	32-<37	
Low birth weight		<2500
Preterm	<37	
Term	37-42	
Normal birth weight		≥2500

As illustrated in Table 1, GA and BW are co-linear measures but not interchangeable, and it is debated which is the better parameter for defining prematurity (19, 20). Prior to the 1990s, ultrasound was not in common use. As delivery dates based on the last menstrual period may be unreliable, reports were mostly based on birth weight (BW) (13, 21). The use of BW as inclusion criterion in studies may have caused inclusion of "preterm-born" individuals that were in fact not born preterm or as preterm as expected, but small for gestational age (SGA).

6.1.2 Increasing survival among preterm-born infants

The first neonatal intensive care unit was established in 1960 by Dr. Louis Gluck in Yale-New Haven Hospital. At that time care of preterm-born infants basically consisted of nutritional assistance, keeping the infant warm and trying to avoid infections (22). Assisted ventilation was introduced in the late 1960s, and endotracheal intubation, monitoring of blood gases, heart rate, blood pressure and respiration became standard of care during the 1970s. New technologies redefined what was considered the limits of viability, gradually decreasing from approximately one kilogram and 28 weeks GA towards the limits we still acknowledge today of 23-24 weeks gestation.

6.1.3 Some major advances in neonatal intensive care medicine

In 1972, Liggins and Howie showed that antenatal corticosteroid therapy administered to mothers with imminent preterm delivery reduced the severity of respiratory distress syndrome by stimulating synthesis of surfactant in the fetal lung (23). Antenatal corticosteroid treatment has been common prophylactic treatment since the early 1980s and has been proven beneficial in randomized clinical trials on infants born at 26-34 weeks' gestation (24).

Treatment with exogenous surfactant was introduced in studies in the mid-1980s, with encouraging results (25, 26). Surfactant reduces alveolar surface tension and prevents collapse of the alveoli at expiration. It is a mixture of lipids and apo-proteins produced

by type II pneumocytes, normally in sufficient amounts from approximately 32 weeks GA. Exogenous surfactant was introduced clinically to prevent or treat respiratory distress syndrome (RDS) in the early 1990s, and was a major reason for improved survival of more immature preterm-born infants in that decade (27-29).

In the 1980s and 1990s several studies indicated that postnatal dexamethasone treatment was associated with shorter duration of oxygen supply and mechanical ventilation, and this treatment therefore became widely used. However, later randomized clinical trials reported severe adverse effects, mainly in the central nervous system. In 2002, the American Academy of Pediatrics stated that postnatal corticosteroids was not recommended for routine use (30), a policy still adhered to. Recent experimental data have questioned if the neurotoxicity is related to dexamethasone itself or to the pharmaceutical excipient sodium sulphite, an issue that will require randomized trials to resolve (31).

Transcutaneous pO_2 and pCO_2 in the 1980s and subsequent pulse oximetry in the 1990s allowed for more exact administration of ventilatory support and oxygen therapy, reducing complications such as retinopathy of prematurity (ROP). With modern cannulas, continuous arterial blood pressure surveillance became routine. Better understanding of the overall needs of preterm-born infants led to more adequate intravenous nutrition and more active and better use of antibiotics, also facilitated by improved equipment for central venous access. The importance of standardization of complex neonatal intensive care schemes, education and quality control was advocated internationally through the Vermont Oxford Network, established in 1989 (32).

Since the turn of the millennium, less invasive methods for assisted ventilation have been advocated. Currently, early administration of surfactant and - if possible - nasal continuous positive airway pressure (CPAP) or even high flow nasal cannulas instead of “traditional” endotracheal intubation with intermittent positive pressure ventilation, is first-line treatment strategy in many NICUs. Combined, these new strategies may lead to less pulmonary barotrauma (33).

This evolution of neonatal intensive care has dramatically changed the limits for what is considered a viable preterm-born infant; a development that has had considerable ethical implications. In England, the Abortion Act from 1967 originally stipulated a 28 week upper GA limit on abortions, a limit that was lowered to 24 weeks in 1990. The issue was brought up again in a parliamentary report in 2006-07, and the limits were principally kept unchanged (34). In Norway, a national consensus conference in 1998 recommended an individual approach to life support for infants born at 23-25 weeks GA (35). Nevertheless, the mean GA threshold reported for resuscitation of a preterm-born infant was 23.0 weeks of GA in 2005 (36).

Better NICU-management has most certainly reduced the long-term negative impacts from being born preterm, and may thereby have led to overall improvements for the preterm-born individuals as a group. On the other hand, better NICU management has also facilitated survival of more extremely immature and vulnerable infants who are at risk of more unfavorable long-term prospects. These two opposing scenarios have operated in parallel since the 1960s and the overall effect is difficult to predict. In retrospect, it seems that a pessimistic scenario may have been prevailing in the early era of NICU care, whereas the more optimistic scenario, i.e. a general improvement with increased survival, took over during the 1980-1990s. Thus, during the last couple of decades, a positive development in survival rates seems to have been paralleled by a decrease in neonatal morbidity, with less septicemia, periventricular hemorrhage, cerebral palsy and chronic lung disease (9, 37). To what extent this will lead to better long-term outcomes remains unknown.

6.2 To be born in the middle of fetal development

Preterm-born infants face a series of challenges related to their immature organ systems and often require major technical and medicinal support. These procedures may be lifesaving in the short-term but injurious in the long-term.

The most obvious challenge in this context is immature lungs. Gas exchange in a 24 - 28 week old fetus normally takes place in the placenta and not through the lung, and

after birth the gas exchange must rely on diffusion through structures that are not meant to become functional until months of further intrauterine development has taken place.

Also the cardiovascular system, neuromuscular structures and sensory organs are at risk of direct injuries, and these organ systems are also in a vulnerable phase of development. They may be harmed by therapeutic interventions as well as by shortcomings within other organs systems, leading to conditions like hypoxic or hyperoxic episodes, blood pressure fluctuations, and under- or mal-nutrition. Negative circles may be established where insufficiencies in one organ system induce injuries in other organ systems and lead to treatment requirements with injurious side effects. When investigating long-term outcomes, this scenario makes it complicated to disentangle causal mechanisms as important factors involved will appear as co-linear in statistical modeling.

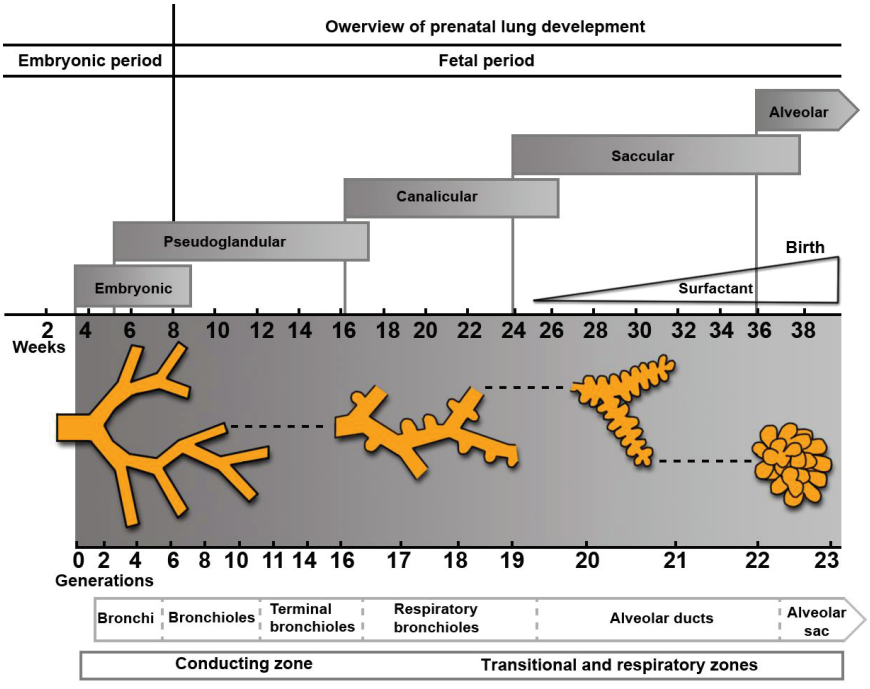
6.2.1 Fetal lung development

The period of organ formation and establishment of the major features of the body is called the *embryonic period* and lasts to the 8th week of gestation, whereas maturation and growth take place in the subsequent *fetal period* (Figure 1). The fetal lung undergoes an ordered process of morphological changes with the end result being an organ capable of performing independent respiration and gas exchange at term (38).

During the *pseudoglandular* stage from week 7-16 of gestation, branching of the main stem bronchi occurs and the divisions of the conducting airways are more or less completed by the 16th week. Cartilage, smooth muscle and major blood vessels begin to form around the larger airway. The *canalicular* stage from week16-24 is a period where the respiratory parts of the lungs are developed. The main characteristic of this period is an alteration of the epithelium and the surrounding mesenchyme. Differentiation from cuboidal cells lining the airways to type II pneumocytes occurs during week 20-22, and type I pneumocytes starts differentiating from type II cells and begin their flattening process that will eventually provide an air-blood interface that

will be capable of performing gas exchange. Lamellar bodies associated with surfactant synthesis, begin to appear in the cytoplasm of type II pneumocytes. Proliferation and invasion of capillaries into the mesenchyme occur and establish the foundation for later exchange of gases between air and blood. By the end of the canalicular stage, the air-blood barrier is just capable to support gas exchange. During the *saccular stage* from week 24 to -35, clusters of sacs are formed on the terminal bronchioles, and alveolar septation commences. The blood-air barrier in the lungs is reduced to three thin layers with type I pneumocytes on one side, a fused thin basal membrane in the center and the vascular endothelium on the capillary side. It is not clear when exactly the *alveolar stage* begins, but probably around 36 weeks of gestation. The alveoli develop from the terminal ends of the sacculi, and their diameter and numbers increase with time through growth and septation. At birth, roughly 1/3 of the alveoli are fully developed. Thus, the final stage of lung development primarily occurs during postnatal life reaching the adult number of 300 million alveoli by two years of age or even later (39, 40).

Figure 1. Lung development



Created by Thor Andre Ellingsen

6.2.2 Lung disease in infancy

Being born early in the saccular stage is a challenge to both bronchial gas transport and the process of gas exchange. Most infants require some form of ventilatory assistance and nearly all require oxygen supplementation to maintain adequate oxygenation. Clinically, the infants appear with respiratory retractions, grunting, tachypnea and cyanosis, a picture labeled respiratory distress syndrome (RDS). RDS is caused by structural and functional pulmonary immaturity, with "stiff" lungs with poor compliance and inadequate capacity for the required gas exchange.

Bronchopulmonary dysplasia (BPD) is a label basically used to define preterm-born individuals who are dependent on oxygen supplementation beyond a certain timeframe. BPD is said to be present if oxygen supplementation is still present at 28 days of age, and the condition is further sub-classified at 36 weeks' GA when BPD is classified as mild if the infant has respiratory symptoms, but no oxygen requirement, moderate if oxygen requirement is less than 30% and severe if the requirement is 30% or more (41).

The pathophysiology of BPD changed in parallel with development of NICU care and the increasing survival of more extremely preterm-born infants. Particularly the introduction of exogenous surfactant was probably important, and the expressions "old BPD" and "new BPD"(42) are often applied to label BPD before and after the surfactant era. Old BPD was primarily related to mechanical injuries inflicted on immature lungs by positive pressure ventilation and the typical picture was pulmonary over-inflation/distention with subsequent inflammatory responses, fibrosis and bronchial muscle hypertrophy in infants that were relatively mature by today's standards. New BPD is seen more as a developmental disorder related to postnatal growth and differentiation of the immature lungs with reduced alveolar numbers, developmental arrest and reduced gas-diffusion area (41).

The pathology of BPD after infancy is poorly described (43, 44). Our understanding of life-long pulmonary consequences of preterm birth and BPD must therefore rely on

indirect assessments and interpretations of physiological and functional examinations, such as exercise physiology.

6.2.3 Vascular changes at birth and patent ductus arteriosus (PDA)

Transition from intrauterine to postnatal life requires major circulatory changes. Preterm birth implies preterm switch from fetal to postnatal circulation before completion of cardiac muscle tissue and vascular structures. There is little knowledge on consequences of this situation, but it is speculated that induction of myocyte hypertrophy (45) and remodeling of the myocardium may alter the final structure of cardiac muscle (46). Lewandowski et.al (47) supported this hypothesis in 2013, presenting findings of distinct differences in both left ventricular mass and function in preterm-born adults.

While intrauterine, blood is shunted around the relatively high resistant pulmonary flow circuit through foramen ovale and ductus arteriosus. After the first breaths of life, the lungs become aerated, pulmonary vascular resistance drops and blood starts flowing through the pulmonary arteries, capillaries and veins. The shunt through the PDA is reversed and the blood that passes is oxygenated, usually leading to its closure during the first 48 hours of life. In a preterm-born infant, closure may not occur due to increased sensitivity of the ductal tissue to the dilating effects of prostaglandins and low sensitivity to the constricting effects of oxygen. Due to the low pressures of the pulmonary circulation, persistence of a PDA results in higher pulmonary blood flow. High blood-flow through an immature pulmonary vascular system can result in acute as well as long-term injurious effects on structure and function, with respiratory difficulties and pulmonary hypertension as a result (48). Half of infants born with BW below 750 gram and 38% of those with BW 751-1000 gram have been reported to have a persistent PDA of perceived clinical significance (49). Traditionally, a persistent PDA with perceived clinical significance was closed. The first attempt of surgical closure was done in 1972 (50) and pharmacological closure with indomethacin was first used in 1976 (51). In the 1980s surgical closure was standard

first line treatment, whereas indomethacin became more widely used in the 1990s. If pharmacological closure did not succeed, a surgical closure was usually done. Optimal therapy for persistent PDA is controversial (52), and in recent years the tendency has been to avoid specific treatment unless strong indications are present (53).

Intimately related to the ductus arteriosus is the left recurrent laryngeal nerve, a branch of the left vagus nerve. The left recurrent laryngeal nerve innervates the intrinsic laryngeal muscles responsible for left-sided laryngeal abduction. The close relation between this nerve and the ductus arteriosus makes it vulnerable to injury during surgical closure of PDA, which is a described risk factor for a paralyzed left vocal cord in preterm-born neonates (54).

6.2.4 Injuries to other organ systems

Brain injuries and neurodevelopmental impairments are among the most feared long-term sequelae to a surviving extremely preterm-born infant. The brain at this stage is vulnerable and at high risk of ischemia and hemorrhages (55). Cerebral palsy (CP) is a permanent motor neural disorder, often also accompanied by other cerebral disorders like epilepsy and/or disturbance of sensory organs, perception, cognition and/or behavior (56). The risk of brain injury increases with decreasing GA (57, 58). Preterm-born children are also at high risk of developing minor neurological dysfunction, not classified as CP, which may involve both fine and gross motor function (59).

Retinopathy of premautiry (ROP) is caused by vascular abnormalities in the immature and developing retina, and hyperoxia is a major risk factor (60). ROP may lead to reduced vision and blindness. Sensorineural hearing loss associated with infections, medicinal treatments or interventricular hemorrhages is also seen in some preterm-born children (61).

The skeletal muscle fibers are not fully developed at time of preterm birth (62), a situation that may have unknown, but potentially long-lasting consequences (63). Fetuses between week 24 and 28 normally move relatively freely in their intrauterine environment, “swimming” in the amniotic fluid. After being born preterm at this stage,

this situation is changed and the fetus/infant is forced to comply with the environment offered by the life in a NICU crib or incubator. We do not know what impact this might have on later neuromuscular development and/or gross and/or fine motor coordination and skills. A research group at Irvine, California, has studied these issues but no conclusions have been reached (64, 65).

Necrotizing enterocolitis (NEC) is caused by necrosis in an immature gastro-intestinal tract, and has been associated with adverse neurodevelopmental outcome (66), especially when surgically treated (67).

From a protected life in the womb, preterms are born into the microbiota of the outside world. They are immunologically unprepared and therefore at high risk of severe infections, which is a very common cause of neonatal mortality and morbidities (68-70) .

6.3 Long-term risks of morbidity after preterm birth

There is a responsibility in moving frontiers. Whereas a lot of research has been invested in improving neonatal survival and short-term outcomes after preterm birth, the long-term outcomes are still uncharted territory. An obvious reason for this unfortunate situation is simply that the first large cohorts of extremely preterm-born individuals only recently have reached early adult life. Hypotheses regarding what will be their health and wellbeing in later life are abundant, but they are basically extrapolations of data obtained from younger preterm-born individuals, supported by developmental knowledge from studies of the general population.

Studies by Barker and colleagues in the 1980s indicated associations between low-BW and later risk of cardiovascular disease (71-73). This resulted in a hypothesis now called ‘developmental origins of health and disease’ (DOHaD) (74) which suggests that adverse influences during intrauterine life lead to permanent alterations in the fetus and predispose to adult diseases (72, 75). The hypothesis has been challenged (76-80), but many studies have confirmed the original observations (81-86), and

support has also been obtained from animal studies (87, 88). Given that preterm birth implies major alterations throughout an important developmental period in early life, it has been argued that the concept of DOHaD is relevant also to preterm-born individuals (89). Studies have e.g. suggested that prematurity is an independent risk factor for high blood pressure (90, 91) and insulin resistance (7, 92). However, these issues are far from settled and more research is required.

6.3.1 Chronic obstructive pulmonary disease (COPD)

We know from population studies that lung function follows a track through a lifespan, and that low lung function in childhood leads to low lung function in adolescence and early adulthood (93, 94). Subsequent to childhood growth, a plateau phase is normally reached at 20-25 years of age, followed by a decline in later life. The maximum level obtained in early adulthood, as well as the timing of onset and the subsequent rate of age-related decline determine when and if lung function impairment and disease will occur in older age. Normally, forced expiratory volume in first second (FEV_1) decreases approximately 30 ml per year (95); however, this varies between individuals for reasons probably related to genetic predispositions and environmental influences, of which cigarette smoking is of major importance. Population studies indicate that bronchial hyperresponsiveness is a characteristic that is related to a steeper age-related lung function decline (93).

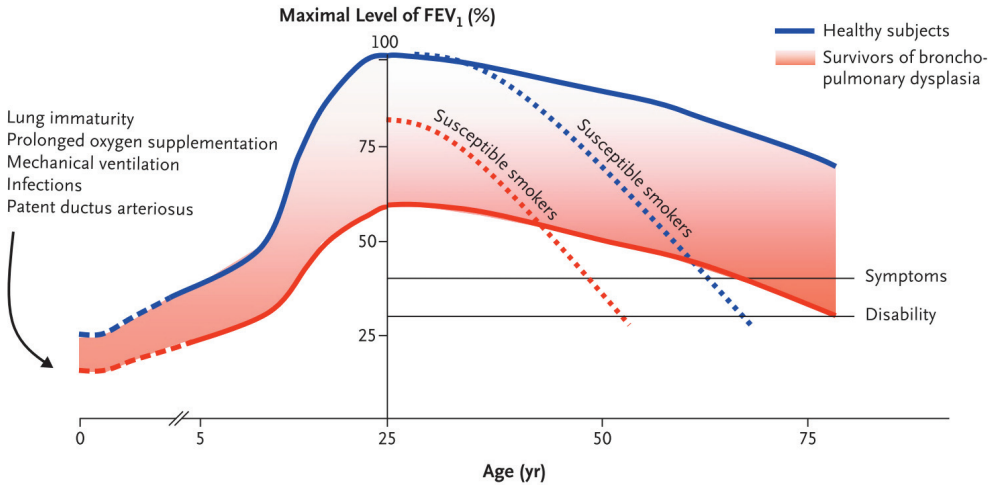
Given a normal age-related decline in an individual who reached normal peak levels in early adulthood, lung function will normally not reach values associated with disability (95). However, the more rapid decline observed in smokers may lead to COPD.

Children and adolescents born preterm have reduced lung function, especially those with a history of lung disease in infancy like BPD (96). It is debated if catch-up growth may occur from childhood to adulthood in these individuals (97). Few studies have reported lung function data in preterm-born adults but those who have, generally report values lower than expected (98-100). Another feature that may be of importance

is increased bronchial responsiveness to methacholine (101-103). Moreover, smoking in this group is a big concern (98, 104).

Thus, suboptimal peak lung function in early adulthood and characteristics associated with a steeper age-related decline in later life, suggest an increased risk of COPD in preterm-born individuals, at least in subgroups (96, 98, 104-107).

Figure 2. Theoretical model of changes in FEV_1 in survivors of BPD and healthy subjects according to age.



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7. SPECIAL INTRODUCTION

As demonstrated by the information presented, preterm birth implies exposures to a range of early life trauma, events and situations that can directly and/or indirectly threaten later health and wellbeing. Promotion of a healthy life style may therefore be particularly important.

In this context, a physically active life may be an important element. However, studies indicate that preterm-born children and adolescents are in fact less physically active than term-born. Moreover, it has not been studied if physical activity in preterm-born individuals lead to similar increases in exercise capacity as observed in term-born individuals. Given the wide variations described for training effects in the general population and the wide range of strains involved in being born preterm, this is not self-evident.

7.1 Physical activity and Exercise capacity in general

Regular physical activity in children and adolescents is important for normal growth and development of aerobic capacity, muscle strength, flexibility, motor skills, and agility (108-110). There seems to be a positive linear relationship between exercise and health outcomes (111). Exercise has an independent protective effect against cardiovascular risk and all-cause mortality, both in the general population and in people with increased risk of cardiovascular disease (4, 112, 113). Early establishment of regular exercise habits in childhood may prevent adult chronic disease like coronary artery disease, hypertension, obesity, osteoporosis and type 2 diabetes (111, 114-116). Most of these diseases reflect lifelong processes that begin during the “pediatric years” (117). Furthermore, physical activity seems to promote self-esteem in children and adolescents, and those who are involved in physical activity seem to have fewer mental health problems (118).

7.2 Tracking of physical activity

Physical activity in adults has probably greater impact on adult health than physical activity during childhood. However; there is reason to believe that a lifestyle characterized by regular physical activity in adulthood is more likely if commenced on early in life.

Some studies have addressed to what extent physical activity track from childhood/adolescence into adulthood (119, 120). Results vary between studies, which may reflect the methods used. Correlations seem to get weaker when the time-spans get longer, as we can see in the Amsterdam Growth study (121). Tracking seems to be stronger in groups at the extremes; i.e., the most and the least active. Sedate behavior seems more likely to persist than active behavior (122, 123).

A large study from Finland recently concluded that a physically active lifestyle develops early in childhood (124). This underscores the importance of establishing an active lifestyle early in life, and to prevent sedentary children and adolescents from becoming sedentary adults.

7.3 The main outcome measure of this thesis – exercise capacity

There are many ways to describe a person's capability to perform physical activity, and the nomenclature is not stringent. Activities involving endurance is often described as aerobic capacity, while the concept "physical fitness" includes both the capability to perform an activity and an athletic body shape. In this thesis, the expression "exercise capacity" is used to describe the ability to perform strenuous exercise over a period of time, which in the studies that are included covers both measurements of peak$\dot{V}O_2$ and distance completed on the treadmill. The concept peak$\dot{V}O_2$ represents the highest amount of oxygen that can be consumed by the body per time unit (3), and is the best objective measure to describe someone's exercise capacity. Peak$\dot{V}O_2$ depends on respiratory and hemodynamic factors as well as the size and functional features and the oxidative enzymatic activity of the exercising muscle.

In adults, oxygen consumption increases with workload and reaches a plateau ($\dot{V}O_2max$). This plateau does not always occur in children, and the highest $\dot{V}O_2$ observed at exhaustion during an exercise test is reported as peak$\dot{V}O_2$ (125), usually expressed in two ways; L/min which indicates the absolute volume of oxygen that the body consumes per minute, and in ($mL \cdot kg^{-1} \cdot min^{-1}$) which takes the person's body weight into account and therefore indicates the potential to move the body during activities performed over time.

7.3.1 VO2 - Fick equation

Adolf Eugen Fick (1829-1901), a German physician, introduced in 1870 what would later be called the Fick principle. The principle explains how to calculate blood flow through an organ, provided knowledge of the amount of a marker substance taken up by the organ in question and the arteriovenous marker substance difference.

Based on this principle one may deduce that the oxygen consumption is cardiac output (the stroke volume (SV) of the heart *times* the heart rate (HR)) *times* the arteriovenous difference:

$$VO_{2max} = SV_{max} \times HR_{max} \times (CaO_2 - CvO_2)_{max}$$

Increased cardiac output and/or increased arteriovenous oxygen difference will increase the maximal oxygen uptake.

With this basis, we can then say that oxygen consumption is influenced by:

- Ventilation – Respiration (gas-exchange in the lung): This represents the entrance of the marker substance (oxygen), where minute ventilation, oxygen diffusion capacity, Hemoglobin (Hb)-oxygen affinity and arterial oxygen saturation play important roles.

- Central blood flow: Cardiac output (heart rate and stroke volume), arterial blood pressure and oxygen transport capacity (Hb) are important factors for transportation of oxygen through the body.
- Peripheral blood flow: Necessary for proper oxygen delivery to the muscles, and includes distribution to active muscles, muscle capillary density and flow, O2 diffusion and extraction.
- Active muscle metabolism: Determines the amount of oxygen the muscles can use. Some important factors are the enzymes and oxidative potential, energy stores and substrate availability, myoglobin concentration, mitochondria size and number, active muscle mass and type of muscle fiber.

7.4 Limiting factors for peak$\dot{V}O_2$

Both central physiological functions (such as pulmonary ventilation and diffusion capacity, maximal cardiac output, and oxygen carrying capacity of the blood) and peripheral physiological functions (as skeletal muscle characteristics and tissue extraction of oxygen) can limit peak$\dot{V}O_2$.

7.4.1 Ventilation

In the general population, limitation of peak$\dot{V}O_2$ is mainly due to cardiovascular limitation, and not lung function. Maximal breathing capacity is a function of maximal tidal lung volume and maximal flow rates in inspiration and expiration. Both volume and maximal flow tend to be based on genetics, and training has little influence (126). Subjects with stronger respiratory muscles are, however, able to create higher tidal volumes and experience less dyspnea (127). Athletes tend to have larger volume and flow; they are able to achieve a smaller end-expiratory and larger end-inspiratory volume and use higher flow rates. It seems likely that this is because of stronger and more fatigue-resistant respiratory muscles (128), but it is probably also related to a positive selection of individuals with a physiognomy that makes them fit to become athletes.

However, different kinds of lung disease may limit peak$\dot{V}O_2$. Those with severe obstructive lung disease have limited exercise capacity, and decline in FEV_1% predicted has been shown to correlate with decline in peak$\dot{V}O_2$ (129-131), especially if FEV_1< 80% predicted, but this correlation is not always obvious (132). Despite the statistical evidence in some studies, this does not prove a causal relationship as FEV_1 in these studies are only one of perhaps several impaired functions in heterogeneous group of individuals.

In a large Finish longitudinal study, the association of physical activity and age-related decline in pulmonary function was investigated (133). The results indicated that physical activity is associated with a slower decline in pulmonary function and with lower mortality, independent of smoking. The effect was greatest among men with the highest levels of physical activity, both in those who had continued high levels of physical activity but also in those who had increased their physical activity from lower levels (133). One of the possible explanation for this is that physical activity may counteract the stiffening tendency in the chest that occurs with increasing age, and enhance inspiratory muscle endurance (134, 135).

7.4.2 Heart and blood flow

Cardiac output has been suggested as the main limiting factor and the primary factor explaining individual differences in peak$\dot{V}O_2$ (3). Heart rate at maximal exercise will not change by endurance training; however, heart rate will be lower at rest and at submaximal exercise. The cardiac muscle increases in both chamber size and wall thickness by endurance training, especially the left ventricle, and results in increased stroke volume. Thus, athletes have a larger stroke volume and lower heart rate at submaximal exercise.

Allocation of more blood to muscles during training is of importance to meet the increased need of oxygen in the muscle. Endurance training induces a moderate increase in plasma volume (136) and later probably also total amount of hemoglobin

(137). This will improve the blood flow through the blood vessels and increase the blood's oxygen carrying capacity.

7.4.3 Peripheral limitations

On local tissue level, factors such as capillary density, various enzymes, mitochondrial size and number and type of muscle fiber (type I or type II), influence the capacity of the muscle to sustain a high level of aerobic exercise. Capillary density in skeletal muscles increases with endurance training, resulting in increased transition time and maintenances of oxygen extraction even at high rates of muscle blood flow (138, 139). Mitochondrial enzyme levels will also increase by exercise, but despite a doubling, only a modest increase in peak$\dot{V}O_2$ has been described (139). Level of mitochondrial enzymes varies among individuals with similar peak$\dot{V}O_2$, and the main effect of the increase is probably to improve endurance performance (140).

7.5 General factors that affect maximal oxygen consumption

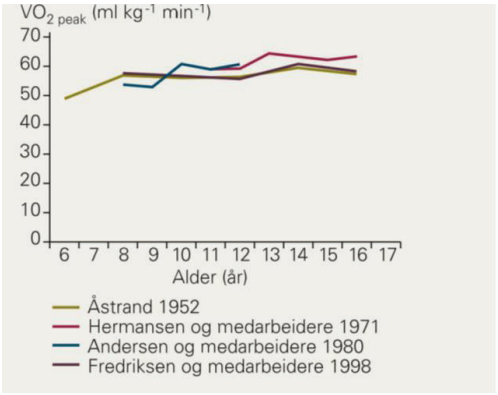
Maximal oxygen consumption depends on:

- State of training: A person's state of training; i.e., participation in physical activity and exercise, is probably *the* single most important factor involved, and contributes substantially to peak$\dot{V}O_2$ in any given individual. The state of training is also related to a range of factors other than those that involve individual biological characteristics. Such factors may be the cultural context and the psychosocial environment in which the individual is living, expectations from society, family and friends, and individual characteristics such as intellectual capacity, motivation and behavioral issues.
- Mode of exercise: Variations between different types of sports regarding the peak$\dot{V}O_2$ obtained generally reflect variations in the volume of activated muscle mass. Treadmill exercise usually produces higher peak$\dot{V}O_2$ values than ergometer cycle exercise (141, 142), and estimated in some studies to be 5-15% higher (143-145).

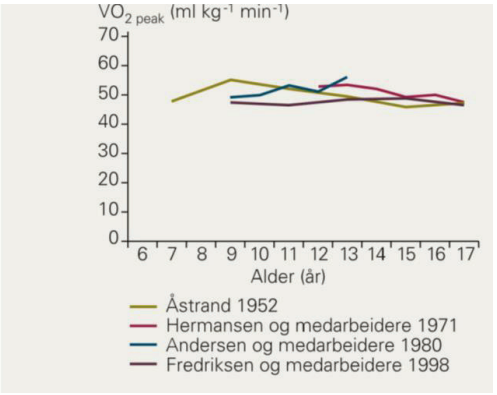
- Heredity: There seems to be individual variations in training responsiveness (146). This may be due to both genotype (natural born gift), and phenotype (function, coordination). Adjusted for age, gender and body mass, it has been stated that the effect of genetics on peak$\dot{V}O_2$ is approximately 30-70% (147-149).
- Body size and composition: Variations in body mass explain nearly 70% of the differences in the maximum oxygen uptake between individuals. Adjusting peak$\dot{V}O_2$ for weight ($mL \cdot kg^{-1} \cdot min^{-1}$) will therefore provide a more accurate measure, and provides additional information when studying inter-individual variations of peak$\dot{V}O_2$.
- Gender: Peak$\dot{V}O_2$ (L/min) increases with the growth of the child. Until 12 years of age, values grow at the same rate in both sexes, even though boys seem to have higher values as early as 5 years of age. Peak$\dot{V}O_2$ increases until 16-18 years in boys and 14 years in girls (125, 150). Before age 10, there are no significant differences in peak$\dot{V}O_2$ between boys and girls, thereafter the differences between women and men are approximately 15-30%. Males have higher peak$\dot{V}O_2$ than females due to more muscle mass, lower fat mass, and 10-14% higher hemoglobin concentration (151). Differences in physical activity (state of training) between boys and girls and between children living in different cultural contexts may also play a significant role. A study from the US reported mean (standard deviation) peak$\dot{V}O_2$ to be 38 (7) $mL \cdot kg^{-1} \cdot min^{-1}$ for healthy 6-11 year old girls and 34 (4) for older girls. For boys, the respective values were 42 (6) for those less than 13 years and 50 (8) for those who were older (152). Norwegian values are reported to be somewhat higher (150) (Figure 3):
- Age (Figure 4): Peak$\dot{V}O_2$ adjusted for weight, starts to decline after 12 years of age in girls, but stays steady in boys until 16 years. In adults, peak$\dot{V}O_2$ declines steadily after age 30, approximately 8% per decade (153). At 60 years of age, an average individual attains about 70% of the peak$\dot{V}O_2$ she or he had at age 25. However, daily physical activity has greater influence on peak$\dot{V}O_2$ than age.

Figure 3. Normal Scandinavian values of peak$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$) during 45 years

Boys:

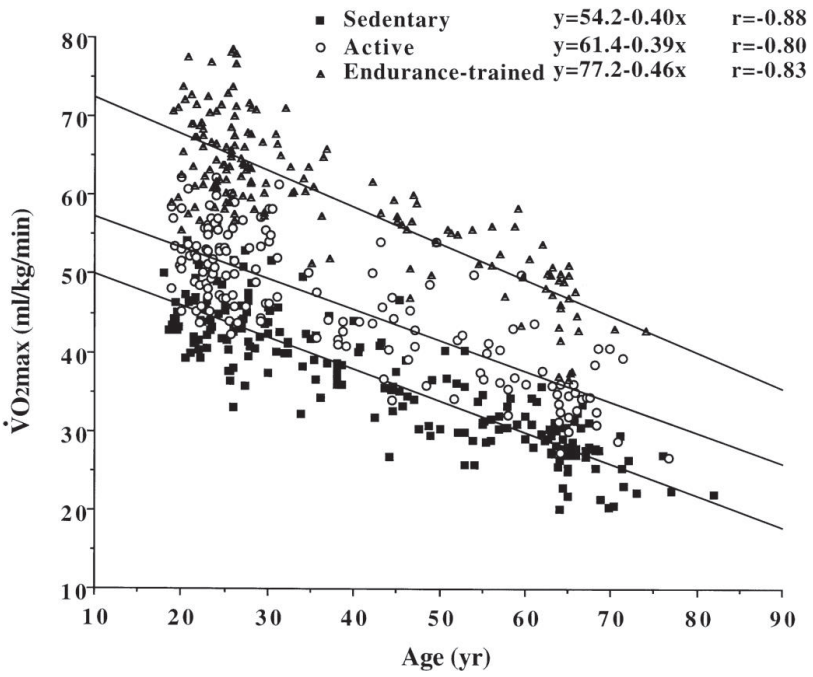


Girls:



Reproduced with permission from Tidsskr Nor Laegefor. Pettersen et.al. (150).

Figure 4. Reduction of peak$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$) in adult men



Reproduced with permission from APS. Wilson et. al. (154)

7.6 Trainability in children and young adults

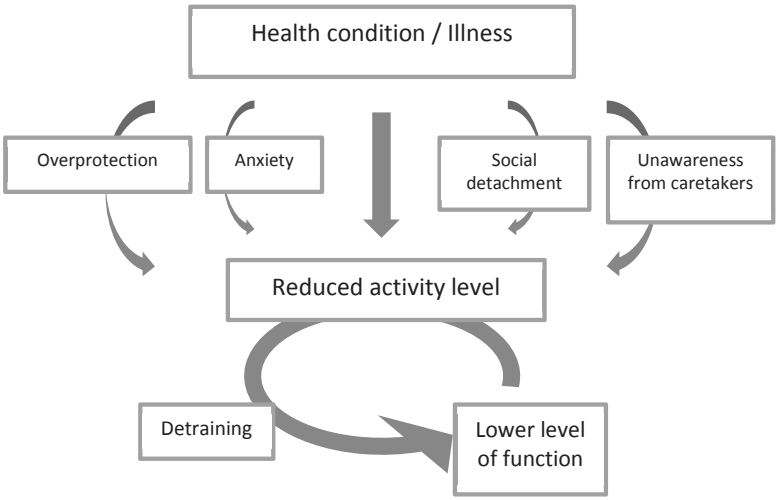
Studies in children have reported minimal or no effects from training on peak$\dot{V}O_2$ (155-157), and it was for a long time believed that pre-pubertal children did not have a response to exercise like that observed in adults. However, recent studies indicate that pre-pubertal and pubertal children in fact can demonstrate training-induced increases in peak$\dot{V}O_2$ (158, 159). A 5-10% increase is typical in children (160), which is lower than generally reported for adults (161). An increase in peak$\dot{V}O_2$ in adults is related to central as well as peripheral cardiovascular adaptions. The arterial-venous oxygen difference does not seem to be influenced by training in children, neither at rest nor at high intensity exercise (162-164). Studies have shown that pre-pubertal children, irrespective of gender, only increase their peak$\dot{V}O_2$ by increasing their stroke volume, and increased stroke volume is explained by an increase in left ventricular internal chamber size and mass after training. (163, 165).

In children, high training intensity has been reported to be necessary to improve peak$\dot{V}O_2$, and heart rates exceeding 80% seem to be required (160), whereas in adults 55-65% have been reported to be sufficient (166). The reason why the effect of training is smaller in children than in adults is not clear. Young people tend to have higher initial peak$\dot{V}O_2$, which can explain some of this phenomenon, as the effect of training is better in those with low than high initial values. There are two main hypotheses. The first is called the overload principle which implies that training programs must exceed what the participant is accustomed to in order for adaptation to occur (167, 168). As children exhibit a higher level of habitual physical activity than their adult counterparts, this situation is harder to achieve. This hypothesis has been both supported (169), and refuted (170). The alternative hypothesis is that there is an optimal age or a maturational stage at which training will be most effective (155, 171) (172-174). The strongest contradiction to the presence of a maturational threshold is the similar influence of training seen in both pre-pubertal and pubertal children (158).

7.7 Factors that affect physical activity in children and adolescents.

Observations from the Canada fitness survey (148) concluded that environmental influence on participation in physical activity is stronger than hereditary, although twin studies have shown that there is a significant genetic effect on a child's general activity pattern (147). Health status is a major determinant for participation in physical activity (Figure 5.).

Figure 5. Factors affecting physical activity



As a group, children with chronic disease or a physical or mental disability are less active than their healthy peers (175). Participation in physical activity requires motor skills, but it is also necessary in acquiring skills, and children and adolescents generally pursue activities where they are competent and successful. Facilitation of physical activity is therefore important, because reduced ability to participate in physical activity may cause deconditioning.

7.8 What do we know about exercise capacity in preterm-born subjects?

As evident from the information presented, preterm-born individuals potentially carry a range of characteristics that possibly can have a negative influence on their exercise capacity. These characteristics can be related to direct injuries or to developmental abnormalities of anatomical structures or physiological processes that are directly or indirectly involved in physical performance. Moreover, the psychosocial environment in which preterm-born individuals grow up and the expectations from society, friends and family, may conceivably contribute to less participation in the strenuous physical exercise required to impact peak$\dot{V}O_2$.

A search strategy including the keywords "preterm, prematurity, exercise capacity, aerobic capacity, $\dot{V}O_2$max and peak$\dot{V}O_2$" was done in PubMed, limited by "English and human". In addition, hand-searched references from included articles were reviewed. Search results where manually assessed and only reports on peak$\dot{V}O_2$ (L/min or mL·kg^{-1}·min^{-1}) in extremely or very preterm-born and ELBW or VLBW subjects where included. The result which includes study characteristics is presented in Tables 2 and 3.

There are four other groups that have reported on *extremely* preterm-born subjects, and 11 groups that have reported on peak$\dot{V}O_2$ in *very* preterm-born subjects. The results differ, but the majority reports a deficit in peak$\dot{V}O_2$ among those born extremely preterm compared to term-born controls. Only three studies report that very preterm-born subjects have a significant deficit. Although the other 8 studies on very preterm-born subjects did not find significant deficits, they still elucidate various limitations related to exercise capacity. The heterogeneity of the studies may be explained by different exercise protocols, different populations of preterm-born studied, different ages at time of testing and differences in neonatal care. For obvious reasons, none of the studies included participants with severe disabilities.
The mean differences between subjects born preterm-born and controls are retrieved from the review of Edwards et al. (176). As seen in the table, peak$\dot{V}O_2$ varies widely, from low to very high values; i.e., from 29 to 49 (mL·kg^{-1}·min^{-1}).

Table 2. Available studies on peak$\dot{V}O_2$ (L/min or mL·kg^{-1}·min^{-1}) in subjects with extremely low birth weight (< 1000 g) or/and born extremely or very preterm compared to controls.

						$\dot{V}O_2$ (mL·kg^{-1}·min^{-1})			
	BW/GA	**Number Preterm /Control**	**Born**	**Age**	**Test**	**Preterm**	**Controls**	**Mean difference**	**Explanation**
Clemm,(177) Norway, 2012	<1000/<28	40/40 35/40	1982-85 1991-92	18 10	Tread-mill	18: 47.1 10: 43.5	18: 49.9 10: 45.7	-2.80 (-6.99, 1.39) -2.20 (-5.70, 1.30)	Deficit. Less PA
Welsh,(178) UK, 2010	<750/<25	38/38	1995	10-11	Cycle	35.3	41.1	-5.78 (-10,53, -1.03) P<0.001	Difference. Poor growth and development Similar PA
Burns,(179) Australia, 2009	<1000/<29	54/55	1992-94	12.5	20m shuttle	42.1	46.1	-4.05 (-6.06, -2.04) P<0.001	Difference. Poor motor coordination
Smith,(180) Australia, 2008	<1000/<32	125/34	1992-94	10-11	20m shuttle	41.6	45.5	-3.90 (-5.55, -2.25) P<0.0001	Difference. Deconditioned and lack of fitness
Kilbride,(181) USA, 2003	<801/<30	47/25	1983-89	11	Tread-mill	31.2	38.5	-7.30 (-10.02, -4.58) P<0.001	Difference. No diff in CLD. Lower level of fitness, perhaps reflection of unrecognized physiologic limitations (cardiac dysfunction?). Lower PA.

Table 3. Available studies on peak$\dot{V}O_2$ (L/min or $mL \cdot kg^{-1} \cdot min^{-1}$) in in subjects with very low birth weight (< 1500 g) or/and born very preterm compared to controls.

						$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)				
	BW/GA	**Number Preterm /Control**	**Born**	**Age**	**Test**	**Preterm**	**BPD**	**Controls**	**Mean difference**	**Explanation**
Joshi,(182) UK, 2013	<1900/<32	62/30	-	8-12	Cycle	35.0	35.4	31.1	3.90 (-0.35, 8.15)	Similar. Lower hours PA. CLD - used greater portion of their ventilator reserve.
Evensen,(183) Norway, 2009	<1500/ 24-35	32/63	1986-88	18	Tread-mill	48.8		48.5	0.30 (-3.19, 3.79)	Similar. Lower in preterm SGA. Less favorable fat distribution. Smokers.
Vrijlandt,(184) Netherland, 2006	<1500/<32	42/ 48	1983	19-20	Cycle	35.3		37.4	-2.10 (-4.88, 0.68)	Difference. Impaired physical fitness. Higher metabolism at rest.
Kriemler,(185) Canada, 2005	500-1500/ 24-30	31/24	1988-1990	5-7	Cycle	29.0	32.0	32.8	-3.80 (-20.85, 13.25)	Similar. BPD higher than VLBW; prematurity. Higher metabolic costs, suboptimal coordination, similar PA.
Pianosi,(186) Canada, 2000	<1200/<28	32/15	1986-87	8-9	Cycle	41.0		46.0	-5.00 (-10.73, 0.73)	Difference. Possibly related to reduced lean body mass. Higher BF.
Gross,(187) USA, 1998	<1550/<31	96/108	1985-86	7	Tread-mill	43.7	41.1	43.2	0.50 (-1.68, 2.68)	Similar.
Jacob,(188) Canada, 1997	<1500/<32	30/13	1981-87	9-13	Cycle	36.7	36.1	37.9	-1.20 (-6.68, 4.28)	Similar. BPD used more ventilator reserve and decrease in SaO2.
Santuz,(189) Italy, 1995	<1400/<30	12/16	1981-87	6-12	Tread-mill		25.2	37.1	-11.90 (-19.64, -4.16)	Difference. Deficits of gas exchange
Parat,(190) France, 1995	<1900/<32	11/5	1986	7,5	Cycle	40.0		41.0	-1.00 (-12.16, 10.16)	Similar. Mild degree of exercise intolerance.
Baraldi,(191) Italy, 1991	<1500/<32	15/26	1976-79	8-12	Tread-Mill	42.9		42.7	0.20 (-5.77, 6.17)	Similar. SGA higher energy cost of running, delayed maturation of muscular coordination.
Bader,(192) USA, 1987	<1200/<29	10/8	1973-79	9-11	Tread-mill		39.1	43.0	-3.90(-14.30, 6.50)	Similar. BPD group achieved normal VO2 at the expense of decrease in SaO2 and increase in PaCO2; pulmonary limitation during exercise.

7.8.1 Potential explanatory factors for deficits in exercise capacity in subjects born preterm

7.8.1.1 Neuromotor function

Various aspects of motor function have been found to be impaired in preterm-born children, like total body coordination and reaction time (193), gross motor functions and visual-motor integration (194, 195). They also have increased risk of minor neurological dysfunction or developmental coordination disorder (DCD), which is defined as "a marked impairment in the development of motor coordination that is not explicable by mental retardation, and is not due to a known physical disorder" (196). Sixty-four percent of preterm-born children had fine motor deficits and 81% had gross motor deficit in a study at 5 years of age (59) compared to 6% of unselected children (197). Even when children born extremely preterm do not show signs of neuromuscular disability, they are found to have low peak muscle power and endurance (198, 199).

Neurological dysfunctions may increase costs of energy when performing exercise and preterm-born subjects may therefore work at a relatively higher percentage of maximal aerobic capacity and thus fatigue at an earlier stage. In addition, a certain level of cognitive skills is required to understand and perform motor tests, and some groups of preterm-born subjects may experience difficulties in that respect (200-207).

Thus, when testing exercise capacity in individuals with a history of preterm birth, thorough reflections are required regarding the validity of the applied test methods; i.e. if the test method is actually testing the characteristics that are under study.

7.8.1.2 Lung function and BPD

Preterm birth and neonatal BPD is associated with reduced lung function in later life, but reports on exercise capacity after BPD have been inconsistent in that both lower (186, 189) and similar (188, 192) peak$\dot{V}O_2$ compared to term-born controls have been found.

Children with a history of BPD are reported to have a high ventilation for a given oxygen uptake, or they are using a higher percentage of their ventilatory reserve during exercise; this is sometimes described to be accompanied also by pulmonary hyperinflation, bronchoconstriction and even arterial oxygen desaturation. Even if peak$\dot{V}O_2$ is reported to be similar to controls in some studies, subjects with BPD may fatigue early, possibly due to a higher metabolic cost of exercise (185, 208) or reduced skeletal muscle coordination, which has been found in children born preterm (193, 199). Resting metabolic rate for children with BPD seems to be normal (209), and high metabolic cost of exercise cannot be explained by excessive resting metabolism.

7.8.1.3 Ventilatory difficulties

Ventilation must increase during exercise, and any ventilatory problem will therefore limit performance. Such factors can be various diseases that indirectly influence ventilatory capacity, poor breathing techniques or psychological causes, and also extra-pulmonary structural airway abnormalities. Thus, in the context of preterm-born, various forms of structural laryngeal abnormalities as well as tracheo-bronchomalacia have been reported (210).

As stated in the general introduction, left-sided laryngeal abduction relies on the left recurrent laryngeal nerve. This nerve runs close to the ductus arteriosus, and injuries to the left recurrent laryngeal nerve after PDA ligation have been described in studies of preterm-born infants and small children (54). However, follow-up studies are rare in early childhood and absent thereafter, and consequences beyond the neonatal period were basically unknown before the present study. The general view held by most researchers seemed to be that a paralyzed left vocal cord does not recover function, but contralateral compensation occurs over time leading to improvement or elimination of symptoms.

Exercise Induced Laryngeal Obstruction (EILO) is a ventilatory problem often confused with asthma (211, 212). Prevalence rates of approximately 5% to 7.5% have been reported in unselected groups of young people, which are nearly comparable to figures reported for exercise induced asthma (213-215). Given the above described scenario with a risk of suboptimal or absent nerve supply to the muscle responsible for left-sided laryngeal abduction, there were adequate reasons to believe that EILO could represent an important cause for respiratory problems in subgroups of preterm-born individuals.

7.8.1.4 Cardiovascular function

Preterm birth has been associated with discontinued growth of the vascular tree with both structural and functional changes (216). Some studies have reported a reduced arterial diameter (217-219), but not others (220, 221). Bonamy et.al. (219) found that children born preterm (GA 25-30) had lower functional skin capillary density. Muscular capillary density is an important determinant of muscle metabolism and also for insulin sensitivity. If lower capillary density is present in other organ systems, various other body functions may theoretically also be affected, like muscular function and trainability. Kilbride et.al. (181) suggested that deficit in peak$\dot{V}O_2$ in preterm-born could reflect unrecognized physiological limitations like cardiac function. However, the authors did not have data to support their theory. Preterm birth leads to an early switch from fetal to postnatal circulation before completion of left ventricular development, and Lewandowski reported in 2013 that adults born preterm had an increased left ventricular muscle mass and significant reduction in systolic and diastolic functional parameters (47). This may possibly contribute to reduced exercise capacity, although a recent study form UK (222) did not find reduced cardiac function in preterm-born subjects.

7.8.1.5 Body composition and muscle fibers

Body composition, fat-distribution and muscle fiber size and/or composition are closely related to exercise capacity and may be altered by preterm birth. There are hypotheses suggesting intrauterine alterations resulting in blood glucose regulation for the benefit of the brain, but at the expense of muscles and muscle growth (223). Altered body compositions with lower fat free mass and smaller muscle size have been described in EP-born subjects (198, 224). The main explanation proposed by Welsh et al. (178) for the exercise deficit demonstrated in the EPICure study, was that EP-born subjects had poor growth and development. Evensen et.al. (183) also stated that preterm-born SGA subjects had less favorable fat distribution, but preterm-born AGA subjects were thinner than controls. Pianosi et.al.(186) explained his results by reduced lean body mass in preterm-born children.

7.8.1.6 Preterm-born subjects and physical activity

As stated previously, the individual level of physical activity is a major explanatory factor for peak VO2. Studies have shown both similar (178, 225, 226) and reduced (181, 227-229) levels of physical activity in preterm compared to term-born or normal birth weight children. Based on the age groups studied, it may seem that participation in physical activity is relatively normal in preterm-born prior to adolescence, but reduced later on (230).

8. HYPOTHESIS AND AIM OF THE THESIS

8.1 The aims of the study

- Compare exercise capacity in preterm-born children, adolescents and young adults, through objective and direct measurements of peak$\dot{V}O_2$ and treadmill running distance with that of matched term-born controls.
- Study changes in exercise capacity from mid-childhood to adolescence in preterm-born and matched term-born controls.
- Study changes in exercise capacity from adolescence to early adulthood in preterm-born and matched term-born controls.
- Search for associations between current lung function and exercise capacity in preterm-born children, adolescents and young adults.
- Search for associations between selected neonatal variables and exercise capacity in preterm-born children, adolescents and young adults.
- Search for associations between physical activity and exercise capacity in preterm-born children, adolescents and young adults, and compare findings with matched term-born control groups.

8.2 The null-hypotheses

a. $H0_1$: There is no difference between preterm-born and term-born subjects regarding exercise capacity in mid-childhood, adolescence and early adulthood.

b. $H0_2$: There is no difference between preterm-born and term-born subjects regarding changes in exercise capacity from mid-childhood to adolescence.

c. $H0_3$: There is no difference between preterm-born and term-born subjects regarding changes in exercise capacity from adolescence to early adulthood.

d. $H0_4$: Exercise capacity in preterm-born subjects is not associated with current lung function.

e. $H0_5$: Exercise capacity in preterm-born subjects is not associated with neonatal factors.

f. $H0_6$: Exercise capacity in preterm-born subjects is not associated with current self-reported physical activity levels.

g. $H0_7$: There is no difference between preterm-born and term-born subjects regarding level of physical activity.

9. ETHICS

The Regional Committee for Medical and Health Research Ethics of Western Norway approved the studies (REK-Vest 2009/1107 - 240.07). Informed written consent was obtained from all participating subjects or from their parents if they were less than 16 years of age.

10. SUBJECTS AND METHODS

10.1 Subjects and Background Data

10.1.1 Extremely premature born subjects

The primary inclusion criterion was GA ≤ 28 weeks. In addition, children with BW ≤ 1000 grams were included, irrespective of GA at birth. All infants born between January 1982 through Descember1985 and February 1991 through June 1992 to mothers who were residents of the counties Hordaland or Sogn & Fjordane in Western Norway at the time of delivery were included. Medical care was provided at the only neonatal intensive care unit (NICU) in the region (Haukeland University Hospital). At the time of inclusion, the two counties had a population of approximately 500.000 and an annual number of births of approximately 6700. Five EP-born subjects in the two cohorts were not born at Haukeland University Hospital, but were transferred sometime during their neonatal period.

To avoid dropouts due to misclassification, a total of 346 charts of infants admitted alive into the NICU and registered with BWs below 1750 grams or GA below 32 weeks had been reviewed. GA was set by the number of completed weeks since the last menstrual period (LMP) and compared to GA predicted by ultrasound scan performed before 21 weeks of gestation, and to postnatal assessment by pediatric examination according to Ballard (231). Scan assessment was preferred if the delivery dates differed more than two weeks and postnatal assessment and if it differed more than four weeks from the date set by LMP. In cases of doubt, a final decision was made by an uninvolved obstetrician with expertise in fetal ultrasound assessments (Prof. Torvid Kiserud).

The mortality rates for eligible infants admitted to NICU in 1982-1985 were 39%, and treatment rates with antenatal and postnatal corticosteroids were 38% and 8%, respectively. Surfactant was not available. For the period 1991–1992, the corresponding mortality rate was 24%, and treatment rates with antenatal and postnatal corticosteroids were 44% and 29%, respectively. Surfactant (Exosurf) was

administrated to 18 survivors (51%) by criteria set by the OSIRIS trial (232) in which the NICU at Haukeland university Hospital participated at the time of inclusion.

A distinction between moderate and severe BPD on basis of oxygen supplementation could not be done. Therefore, BPD was classified as mild if oxygen treatment was required at 28 days of age, but not at 36 weeks postmenstrual age (PMA) and moderate/severe if oxygen supplementation was still required at 36 weeks' PMA. Thus, three strata of BPD were defined: none, mild, and moderate/severe. Further stratification was not considered due to the limited number of subjects.

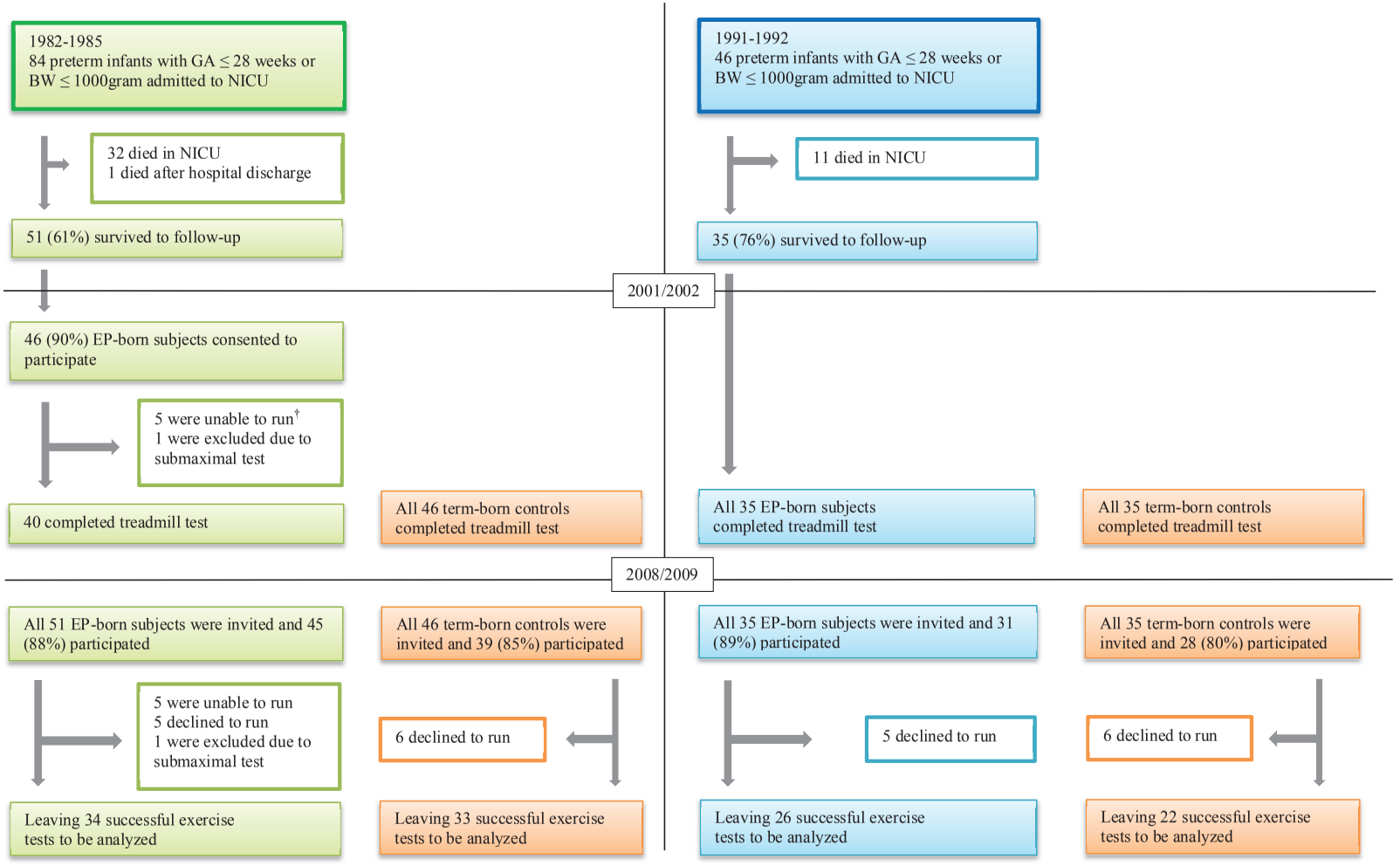
There were 51 and 35 eligible EP-born survivors from the 1982-85 and the 1991-92 periods, respectively. The two cohorts had mean ages of 10.6 and 17.7 years when first examined by professor Thomas Halvorsen in 2001/2002 (233), and 17.8 and 24.9 years when examined by Hege Clemm in 2008/2009. Participation and attrition rates are given in Figure 6. Medical history and past diagnoses and treatments were obtained at the clinical examination performed by a pediatrician (T.H. or H.C.) and from hospital records. Blindness, deafness, quadriplegic cerebral palsy or serious psychiatric disorders were classified as major disabilities. Disabilities not preventing attendance at regular schools were classified as minor.

10.1.2 Term-born controls

For each child born EP, the subsequent birth of the same gender and BW between 3 and 4 kg (Norwegian 10–90 centiles) was selected as a term-born control. If that subject declined, the next-born subject was asked, and so on. To ensure objectivity in the selection process, an uninvolved but trained medical secretary did this job with the following two criteria given for exclusion: home address more than one hour drive from Haukeland University Hospital and registered diagnoses of mental or physical disability likely to interfere with the test situation. Only one subject with a severe lung condition for which she later received a transplant was excluded due to these criteria.

To complete a full 1:1 matched control group, an average of 1.3 term-born subjects had to be asked. Control subjects were not matched with the EP-born subjects for indicators of socioeconomic status. However, the educational level of parents of EP-born subjects and term-born controls eventually participating revealed no significant differences.

Figure 6. Cohorts – with flow chart



10.2 Study design

This was a longitudinal controlled cohort study. EP-born participants were defined *after* the event of interest had occurred (preterm birth), implying a historical design. However, antenatal, perinatal and neonatal data were recorded in the patient's charts *before* outcome was assessed, and in this respect the design was historical and prospective.

The present thesis reports results from the examinations performed both in 2001-2002 and in 2008-2009. At both examinations subjects were seen twice within a two weeks period, and the exercise testing was performed on the first test-day. If a respiratory tract infection or an asthma event were reported within two weeks before the examination, participants were rescheduled. Long acting β2-agonists were stopped two days before testing and short acting β2-agonists and inhaled corticosteroids were stopped from at least 24 hours before testing. No subjects were on leukotriene blockers.

10.3 Pulmonary Function

Pulmonary function was measured with Vmax 22 spirometer (*SensorMedics inc, Yorba Linda, CA, USA*), applying standard quality criteria (234). Calibration of the flow sensor was performed prior to each test in accordance with automated procedures and the instructions given by the manufacturer, that were also in accordance with the American Thoracic Society (ATS) requirements for diagnostic spirometers. A bacterial filter (*MicroGard, SensorMedics inc., Yorba Linda, CA, USA*) with an attached mouthpiece was used. Subjects were tested seated in an upright position with the face pointing straight forward, supporting the cheeks in their hands and wearing nose-clips. Test-maneuvers were repeated until at least three technically acceptable measurements were obtained. In the final report, the highest forced expiratory volume in first second (FEV_1) and the highest forced vital capacity (FVC) obtained from technically acceptable flow-volume loops were recorded, whereas forced expiratory flow at 25-

75% of FVC (FEF_{25-75}) was obtained from the loop with the highest sum of FEV_1 and FVC. Measured values were expressed as percentage of predicted using the all-age reference equation, correcting raw data for differences in age, sex and height (235). FEV_1 x 35 was used to calculate maximal ventilation (VE_{max}) (236). The same experienced technician performed all tests, blinded to results obtained in any previous test session.

10.4 Exercise Test

The same set-up for exercise testing was applied in all participants at both examinations by the same respiratory physiologist using basically the same equipment and the same computerized test protocol An incremental treadmill (*ELG 70; Woodway, Weil am Rhein, Germany*) exercise test was applied. Calibration of the flow sensor was performed prior to each test in accordance with automated procedures and the instructions given by the manufacturer. After baseline variables had been established, subjects ran to exhaustion wearing a face mask connected to a Vmax 29 cardiopulmonary exercise unit (Sensor Medics, Yorba Linda, CA, USA). To make the subjects familiar with the treadmill and to optimize the conditions for cardiopulmonary exercise testing, a modified Bruce protocol was used (237) where speed and elevation gradually increased every 90 seconds from an initial slow-walking phase. The test was stopped when the subject indicated exhaustion, preferably supported by a plateau in oxygen consumption or heart rate response (238, 239). Variables of gas exchange and airflow were measured breath-by-breath, averaged over 10 seconds, and the highest values determined during the last 60 seconds were taken as maximal values. Oxygen uptake (peak$\dot{V}O_2$), carbon dioxide production (peak$\dot{V}CO_2$), tidal volume, respiratory rate and heart rate were measured directly, whereas maximum minute ventilation (VE_{max}) was calculated from tidal volume (V_t) and respiratory rate (RR). $\dot{V}O_2$ at the ventilatory threshold, here defined as the anaerobic threshold (AT), was obtained from the inflection on the VCO_2/VO_2 plot, with support from the $VE/\dot{V}CO_2$ and $VE/\dot{V}O_2$ plots (238). Calculation of ventilatory reserve at maximum exercise was based on the assumption that $FEV_1 \times 35$ was the predicted VE_{max} (236). Exercise performance in the

test situation was described by the "distance completed on the treadmill" (meters), measured directly through the computerized protocol.

10.5 CLE-test

In paper #4 we examined the larynx during exercise, and used a set-up described by our group in 2006 (240). The equipment consisted of a headset and a facemask (*Hans Rudolph inc., Wyandotte, USA*) adjusted in order to secure the flexible fiberoptic laryngoscope with diameter 3.6 millimeters and length 255 millimeters (*Olympus ENF-P3, Tokyo, Japan*) to the head. A video system (*Telecam, Karl Storz, Tuttlingen, Germany*) was connected to the flexible fiber optic laryngoscope. The same exercise protocol as described in chapter 10.5 "Exercise Test" was used. The method was established in cooperation between the Department of Otolaryngology, Head and Neck surgery and Department of Pediatrics, and was called the Continuous Laryngoscopy during Exercise – test (CLE-test).

10.6 Demographic Variables and Questionnaires

A questionnaire was used to obtain general background variables, health related information and exercise habits. Two validated questions served to determine the level of leisure-time physical activity (*www.ecrhs.org*) (241): (1) Apart from at school, how often do you usually exercise so much that you get out of breath or sweat? and (2) apart from at school, how many hours a week do you usually exercise so much that you get out of breath or sweat?

The response options were:

(1) Times: Never, less than monthly, 1-3 times monthly, once weekly, 2-3 times weekly, 4-6 times weekly and daily.

(2) Hours per week: Less than ½ hour, ½ hour, 1 hour, 2-3 hours, 4-6 hours and 7 hours or more.

Drop-outs reduced the participation rates at the second follow-up, and some of the categories were merged:

Times: <1 time or less per month, 1-4 times per month, 2-3 times per month and 4 times or more per month.
Hours per week: ½ hour or less per week, 1-3 hours per week, 4 hours or more per week.

10.7 Statistical analyses

The study was designed as a 1:1 matched controlled cohort study with matching of controls according to gender and time and place of birth of the EP-born index subject. All analyses were performed using SPSS version 21 (SPSS, Chicago, IL).

The main outcome variables were peak$\dot{V}O_2$ and "distance completed on the treadmill" (meters). Group means and standard deviations, medians and ranges were calculated by descriptive analyses. In the first follow up presented in paper #1, univariate analyses and paired t-tests were used to compare group means. Otherwise, paired multivariate two way analyses of covariance was mostly used to assess group differences and relationships between multiple explanatory variables and continuous numerical outcome-variables (mixed linear model of SPSS). With this model, also pairs with drop-outs contribute to the statistical analyses, without reducing the number included. This model was used at the second follow-up for paired analyses between EP and term-born groups and for longitudinal analyses of repeated data adjusted for gender. Reported physical activity was compared using ordinal logistic regression (generalized estimating equations model of SPSS). Associations between explanatory variables and outcome in various subgroups were compared using interaction terms.

The chi square test was used to compare categorical data, such as number of subjects in the various strata of physical activity. To test correlation between exercise capacity at first versus second follow-up, a general linear regression model (ANCOVA) was used, and the explained proportion of variation in outcome was reported as the squared regression coefficients (R^2).

Exercise capacity in relation to lung function and BPD was analyzed using one way ANOVA, split by EP vs. term-born subjects and adjusted for gender.

Associations between exercise capacity and neonatal variables were tested using a backward stepwise general linear regression analysis, adjusted for gender. The following perinatal variables were included in the analysis: GA at birth, BW, duration of ventilator treatment (days), duration of neonatal oxygen treatment (days), antenatal maternal treatment with corticosteroids, postnatal treatment with corticosteroids, smoking during pregnancy, single or twin birth, vaginal or caesarian section, closure of patent ductus arteriosus and postnatal septicemia.

10.8 Statistical power

Statistical power refers to the probability of a study of being able to reject the null hypothesis when it is false, or alternatively, to accept the alternative hypothesis when it is true. Statistical power basically depends on the number of participants included, the distribution of the outcome measure in the groups that are under study, the minimum effect size (group difference) that is considered to be of interest, and the significance level that is required.

The original project was in 2001 designed to address a series of outcomes, with variables that had different and partly unknown distributions. By nature, a priori sample size calculation becomes complex in this setting.

The sample size was calculated in order to detect a clinically relevant decrease in the EP-born groups for the main outcome measure for the overall study, which was FEV_1. The study populations were defined to achieve 90% power to detect a difference in FEV_1 of at least 7.5% between those born EP and at term, providing a 5% significance level. Splitting the data-set by BPD or by gender would by nature reduce the number of subjects in the groups and therefore also compromise the statistical power of such sub-group analyses.

With respect to the outcome variables used to describe exercise capacity, the studies had approximately 80% power to detect group differences (EP vs. term-born) in the range of 3-4 $mL \cdot kg^{-1} \cdot min^{-1}$, providing 5% significance level, which was considered adequate. These issues will be discussed further in the Discussion section.

11. RESULTS

11.1 Subjects

At first follow up in 2001-2002, there were 40 successful paired exercise tests to be analyzed in the 1982-85 cohort, and 35 in the 1991-92 cohort (Figure 6.). At second follow up in 2008-2009, corresponding numbers were 34 EP-born and 33 term-born from the 1982-85 cohort, and 26 EP-born and 22 term-born from the 1991-92 cohort.

11.2 Exercise capacity

At first follow-up in 2001-2002 when 18 and 10 years of age, respiratory quotient RQ ≥ 1.05 or maximal heart rate HR ≥ 95% predicted was achieved by all term-born and 88% of EP-born participants of the 1982-85 cohort, and by 91% of term-born and 71% of EP-born participants of the 1991-92 cohort. At second follow-up in 2008-2009 when 25 and 18 years of age, corresponding values were achieved by all term-born and all but one EP-born participant of the 1982-85 cohort, and by 91% of term-born and 92% of EP-born participants of the 1991-92 cohort.

At first follow-up, mean peakVO_2, expressed as L/min and and distance (meter) completed on the treadmill were significantly reduced by 9-16% in EP-born subjects compared to term-born controls in the two birth-cohorts. There was an insignificant reduction in mean peakVO_2 ($ml \times kg^{-1} \times min^{-1}$) by 5% for the EP-born subjects in both birth-cohorts.

At second follow-up of the 1982-85 cohort (age 25 years), mean peak$\dot{V}O_2$ reported as L/min and $mL \cdot kg^{-1} \cdot min^{-1}$ and distance (meter) completed on the treadmill, were significantly reduced by 8-11% in the EP-born compared to the term-born group.

At second follow-up of the 1991-92 cohort (age 18 years), mean peak$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$) were 7% lower in the EP than the term-born group, whereas mean peak$\dot{V}O_2$ (L/min) and distance (meter) completed on the treadmill were significantly reduced by 11% and 10%, respectively.

Adjustment for asthma did not change the results, but adjustment for self-reported smoking led to greater differences between the EP-born and term-born groups at second follow-up.

11.3 Exercise capacity in relation to disabilities

As described, some participants with major disabilities were unable to run. Excluding EP-born participants with disabilities, but nevertheless capable of running, altered statistical conclusions only at second follow-up for the 1991-92 cohort (age 18) rendering the difference in peak$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$) between the EP and term-born group statistically insignificant (44.1 vs 45.3; $p = 0.416$).

11.4 Exercise capacity in relation to gender.

In general, females and males scored differently on several of the parameters related to exercise capacity, but interaction terms revealed no significant gender differences regarding difference between those born EP and at term in any of the outcomes. However, sub-group analyses suggested that differences between the EP and term-born groups seemed to be larger for the males. As exercise capacity is strongly related to gender, all group comparisons were adjusted for gender.

11.5 Exercise capacity in relation to neonatal variables.

At first follow-up distance completed on the treadmill (meters) was negatively associated with postnatal treatment with corticosteroids for lung disease ($\beta = -187$ meter, $p = 0.013$ (adjusted for gender). At second follow-up this association remained significant for the 1991-92 cohort ($\beta = -242.5$ meter, $p = 0.014$), but not for the 1982-85 cohort. No significant associations were observed between other neonatal variables and the main outcome variables, notably also not for neonatal BPD.

Neonatal history did not differ for the different categories of reported physical activity.

11.6 Exercise Capacity in relation to FEV_1 and BPD

Mean FEV_1 % predicted was significantly reduced in the EP-born compared with the term-born group whereas FVC % predicted was not. Moreover, mean FEV_1 was significantly and negatively associated with increasing severity of neonatal BPD. Splitting FEV_1 % predicted into quartiles revealed no associations with peak$\dot{V}O_2$ or distance completed in subjects born EP in any of the cohorts at any of the two follow-ups. Moreover, there was no association between exercise capacity and the three BPD strata in any of the cohorts at either follow-up.

FEV_1, ventilatory reserve capacity, smoking and use of asthma medications did not differ for the different levels of reported physical activity.

11.7 Exercise capacity and level of activity

At first follow-up (10 and 18 years), there was a significant difference in reported physical activity between EP-born and term-born participants. Physical activity 2-3 *times* per week or more was reported by 34% EP-born and 72% term-born controls ($p < 0.001$) and 2-3 *hours* per week or more by 36% of EP-born and 59% of term-born controls ($p = 0.004$), when both cohorts were analyzed together.

At second-follow up (18 and 25 years), this trend of less physical activity among those born EP could still be seen, but differences were statistically insignificant.

Reported physical activity was similarly and positively associated with peak$\dot{V}O_2$ in the EP-born and term-born groups, and peak$\dot{V}O_2$ increased with increasing activity level in all age groups except that no such associations were observed in neither the EP-born nor the term-born group at 10 year of age (the 1991-92 cohort).

11.8 Changes in Exercise Capacity from 10 to 18 years

Development from first (10 years) to second (18 years) follow-up was similar for the EP-born and term-born groups for all the assessed variables (tests of interaction). There were significant increases in weight, height, peak$\dot{V}O_2$ (L/min), distance

completed in meter and VE_{max}, and significant decreases in HR_{max} and max respiratory rate. There were no significant change over time in AT and peak$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$). There were gender differences in that females had larger increases in weight ($p = 0.003$) and in height (< 0.0001) and males had larger increases in VE_{max}, AT, and peak$\dot{V}O_2$ (L/min) ($p = 0.001$ for all). These gender differences were similar for those born EP and at term.

Reported leisure time physical activity did not change from first to second follow-up, for neither EP-born nor term-born subjects, and there were no interaction effects between the two groups and time, indicating a similar development for the two groups.

At first follow-up of the 1991-1992 cohort at age 10, there were no association between peak$\dot{V}O_2$ and reported physical activity for either group, but at second follow-up at age 18, positive and similar associations between peak$\dot{V}O_2$ and reported physical activity were observed for both the EP-born and term-born participants.

There were significant associations between measures of exercise capacity obtained at 10 and 18 years of age; for peak$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$) coefficient of determination (R^2) = 0.217, $p = 0.031$, peak$\dot{V}O_2$ (L/min), $R^2 = 0.529$, $p = 0.010$, and distance completed (meter), $R^2 = 0.253$, $p = 0.034$.

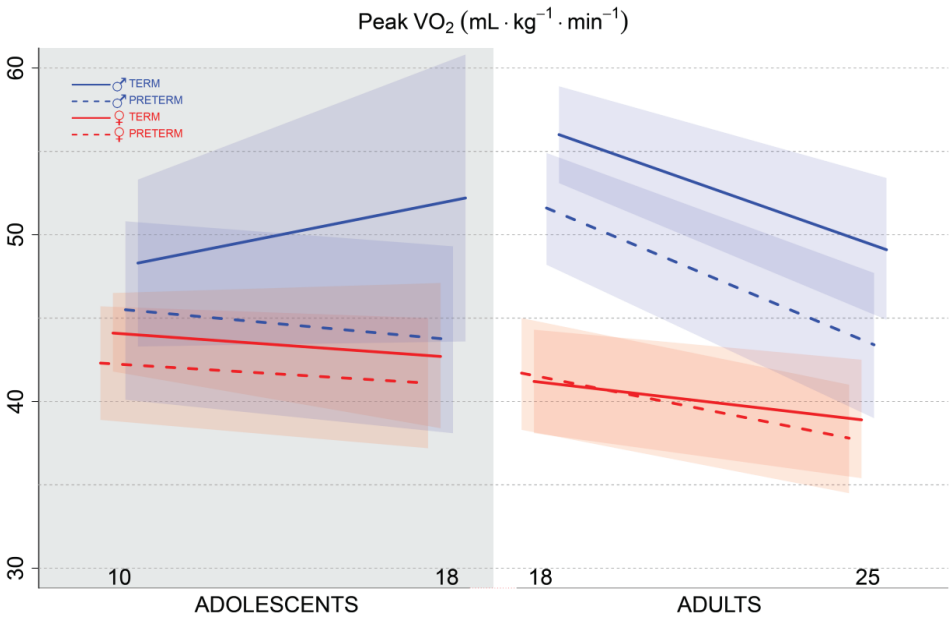
11.9 Changes in exercise capacity from 18 to 25 years

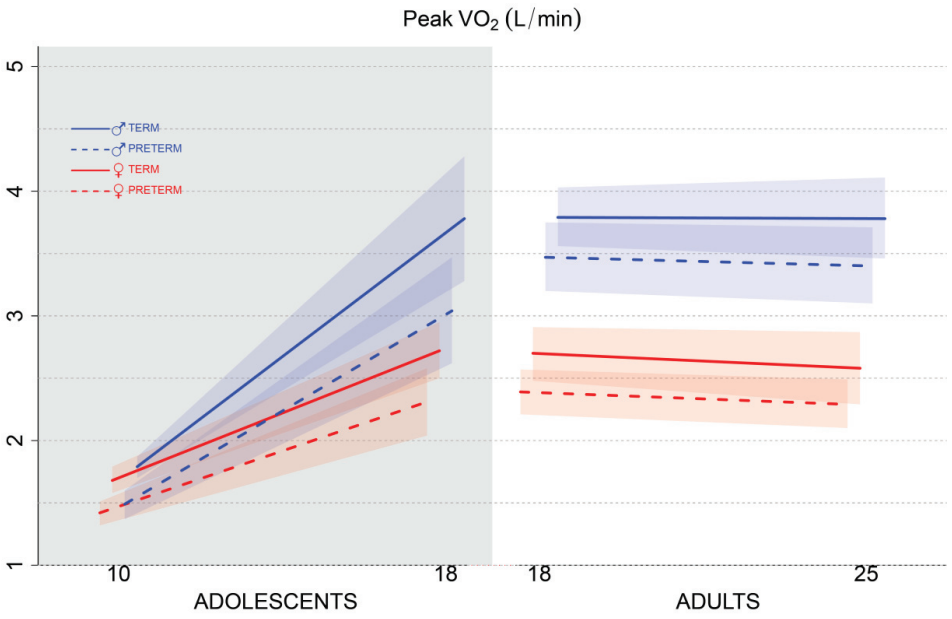
Development from first (18 years) to second (25 years) follow-up was similar for the EP- and term-born group for all the assessed variables (tests of interaction). There were significant increases in weight and anaerobe threshold in percentage of predicted peak$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$), and insignificant increases in height, peak$\dot{V}O_2$ (% predicted) and ventilatory reserve. There were significant decreases in maximum heart rate, minute ventilation at max (VE_{max}/kg; $mL \cdot kg^{-1} \cdot min^{-1}$), peak$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$), distance completed and respiratory rate and insignificant decreases in $\dot{V}O_2$ at AT ($mL \cdot kg^{-1} \cdot min^{-1}$) and peak$\dot{V}O_2$ (L/min).

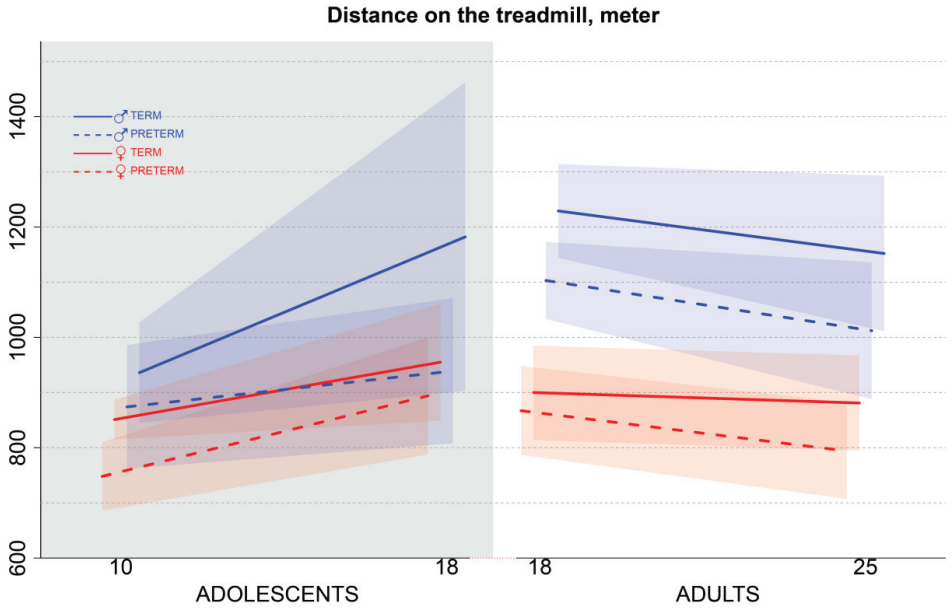
Reported leisure time physical activity tended to increase from first to second follow-up for both the EP and term-born groups in hours per week; β = 0.721 (95%CI; 0.22, 1.22), p = 0.005. There were no interaction effects between the two groups and time, indicating a similar development.

There were significant and strong associations between measures of exercise capacity obtained at 18 and 25 years of age; for peak$\dot{V}O_2$ (mL·kg^{-1}·min^{-1}) R^2 = 0.623, for peak$\dot{V}O_2$, (L/min) R^2 = 0.811 and for distance completed (meter) R^2 = 0.596 (p < 0.001 for all three analyses).

Figure 7. Changes in Exercise Capacity




Peak VO_2 (L/min)
5
4
3
2
1
♂ TERM
♂ PRETERM
♀ TERM
♀ PRETERM
10
18
ADOLESCENTS
18
25
ADULTS


Distance on the treadmill, meter
1400
1200
1000
800
600
♂ TERM
♂ PRETERM
♀ TERM
♀ PRETERM
10
18
ADOLESCENTS
18
25
ADULTS

11.10 Findings at age 18 in the 1982-85 vs. the 1991-92 birth cohort

Peak$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$) in 18 year old subjects born EP in 1982-85 was higher than in comparable subjects born in 1991-92 (β=4.2, 95% CI; 0.38,8.02, p=0.032, adjusted for gender), but not so for the term-born control group (β=0.34, 95%CI; -3.62,4.29, p=0.865, adjusted for gender). As depicted in Figure 7, the data suggest that this effect was explained mainly by the EP-born males. However, this apparent cohort difference was not statistically significant (test of interaction, p=0.330 adjusted for gender). All other exercise outcomes were similar in the two birth-cohorts. There were also no differences in height or weight.

11.11 PDA ligation and left vocal cord paralysis

Thirteen EP-born subjects from the 1982-85 cohort had a history of neonatal surgical closure of PDA. Laryngoscopy was performed in 11 of those who had a ligated PDA, and seven of them had left sided vocal cord paralysis (LVCP). These subjects had significantly more reported respiratory symptoms and lower values for FEF_{25-75} and FEV_1/FVC than the EP-born subjects without LVCP. They had inspiratory stridor during exercise, but exercise capacity was nevertheless unrelated to LVCP.

Neonatal BPD developed in six of the seven with LVCP, in two of four who had their PDA ligated without developing LVCP and in only three of 33 of the EP-born who did not undergo PDA ligation. When comparing the 6 subjects with BPD and LVCP with those with BPD without LVCP, LVCP seemed to explain most of the airway obstruction in subjects with BPD although the numbers were too small for meaningful statistical comparison.

12. DISCUSSION

12.1 Methodological considerations

12.1.1 The study groups

The purpose of clinical research is to generate generalizable knowledge based on the population sample that is under study. To achieve this aim, the subjects under study must represent an unbiased sample of the larger population the study aims to describe.

In many studies pertaining to present follow-up data for preterm-born subjects, inclusions have been based on BW alone. Although BW and GA are co-linear measures, population samples based on BW will necessarily encompass a variable and unpredictable proportion of individuals who are small for gestational age (SGA). In the present study, the main focus of the inclusion algorithm was preterm birth and GA. However, we know that delivery dates set solely by the last menstrual period (LMP) of the mother is not fully reliable, and can in some cases miss by several weeks. In the 1980s, ultrasound scans were not routinely performed to set delivery dates. Thus, in order to include all subjects considered extremely preterm-born within the time periods under study, subjects with BW 1000 grams or lower were also included, irrespective of GA. This strategy was clearly not optimal, but nevertheless preferred to the alternative, which was inclusion based solely on GA set by LMP. There were three subjects included on the basis of BW equal to or less than 1000 grams but GA above 29 weeks in the first birth-cohort and two in the second. Overall, the number of subjects with BW < 10^{th} centile according to the reference values used at the time of inclusion (242), were 9 in both the 1982-85 and the 1991-92 cohort.

Bearing in mind the DOHaD concepts, to be born SGA may have implications for later exercise capacity, but few studies have explored this issue. There were no effects from SGA in relation to exercise capacity in our study sample; however, we cannot draw firm conclusions due to the small number of participating SGA subjects.

Population studies will always be influenced by various confounding factors, known and unknown. Norway has a relatively egalitarian societal structure compared to many other countries, with free access to health care for all children. Despite no active

matching on social class, we found no significant differences in educational level between the families of the EP and term-born participants. All mothers of the EP-born participants were residents of a defined geographical area, and to the best of our knowledge, no eligible neonates were born outside this area during the inclusion period without subsequent transfer and thereby inclusion. This makes the study truly population based and less likely to be influenced by confounding factors than studies recruiting from particular hospitals or institutions.

To recruit unbiased and representative control subjects is essential for the quality of any clinical research. Studies that rely on recruitment from friends of the study group, medical students from the local university or friends or children of colleagues and staff working in the hospital (243), are at risk of bringing together a group of people that is not representative for the general background population, a situation that may highly influence the statistical conclusions of the study. Openly inviting classroom friends of the index subject, which is a strategy sometimes applied in studies, in fact means that 20-30 subjects are asked to participate, with a high risk of recruiting a biased group of people due to inclusion of subjects with a personal interest in being tested. We chose a strict system for recruitment of control subjects, based on the "next-born-subject" principle. Sixty-one (75%) of the primarily invited control subjects responded positively and on average 1.3 subject were asked per index subject, facts that make the likelihood for inclusion bias low. Only one term-born subject was excluded, a patient with a severe chronic lung disease who later required a transplant. We therefore hold the control group to be representative of the general term-born population from which the EP-born index subjects were recruited.

Selection bias of the EP-born index subjects due to preferential survival at the NICUs is difficult to exclude. Survival rate was 61% in 1982-85 and 76% in 1991-92. This is similar to reports from other comparable populations in similar institutions at that time (2). We have no reason to suspect that mortality differed in our institution compared to other institutions; however, to address the question of skewed or preferential survival we would have had to assess neonatal data also for subjects not surviving, which was not done.

The study design was originally cross sectional, and was later changed into a longitudinal design. The quality of longitudinal studies critically depends on low drop-out rates or at least unbiased drop-outs. In similar studies, the ratio between subjects actually examined versus the number of subjects eligible for inclusion has been rather low or not reported on (178, 180, 185). In the present study at first follow-up, participation rate was 90% for EP-born in 1982-85 and100% for EP-born in 1991-92. At second follow-up, corresponding figures were 88% and 89%. However, not all were able or willing to perform the exercise test, and the fraction who eventually completed at first follow-up was 78% for EP-born in 1982-85 and 100% for EP-born in 1991-92, with corresponding figures being 67% and 74% at second follow-up (Figure 6.). Despite a high participation rate, there is therefore a risk that attrition might have biased the conclusions, particularly at second follow-up when there was a tendency for both EP and term-born controls to refuse the treadmill test. Those who refused tended numerically to have lower exercise capacity at first follow-up in both the EP and term-born group; however, this difference was not significant. As this phenomenon was similar in both the EP and term-born group, it probably did not influence statistical conclusions.

Overall, we hold our EP-born and term-born groups to adequately represent unbiased samples of similarly EP-born and term-born subjects in general. External validity refers to the extent to which the results of a study can be generalized to other situations and to other people (244). Thus, data from these samples can be used to make inferences regarding outcomes for other preterm-born individuals.

12.1.2 Gender

Deficits in exercise capacity seemed to be explained mainly by low capacity among the EP-born males; however, the study was not designed to explore effects from gender and therefore the number of participants was too low to study this issue with sufficient statistical power. Nevertheless, statistically significant differences between EP-born and term-born males were observed in most of the analyses, whereas differences between EP-born and term-born females generally tended to be smaller

and not statistically significant. These data support findings from other studies, including studies from our own group, reporting an advantage for EP-born females regarding several factors ranging from survival to quality of life (245, 246). However, when these apparent gender differences regarding exercise capacity were formally tested using interaction terms, the apparent differences between EP vs. term-born males and females were not statistically different. In retrospect, more subjects should have been included. Our study can propose that there *may be* a gender effect, and suggest that this is a research field that deserves more attention.

12.1.3 Test conditions

When testing exercise capacity in EP-born subjects, thorough reflections are required regarding the validity of the applied test methods, i.e. if the method is actually testing the characteristics that are under study.

There are several methods used for exercise testing, among which are cycle ergometer, 20 meter shuttle run test and treadmill test. For each test set-up various protocols may be applied. We used treadmill testing because walking and running are familiar to most people and also highly relevant for daily life. Moreover, it is easier to push the test-person to exhaustion on a treadmill compared to on a cycle ergometer, particularly a child, and treadmill exercise does not require the kind of attention and cooperation of the 20m shuttle run test. Sensory, cognitive and neuromotor disabilities are well described sequelae of extreme preterm birth, and "exercise experience" may be reduced in this group. Therefore, the test set-up was kept simple and straight forward in order to minimize the risk of making biased conclusions regarding exercise capacity *per se*. The treadmill was run according to an identical modified Bruce protocol for all participants. This protocol has an initial period at walking pace, before speed and elevation increases in a predictable manner until maximum exercise capacity is reached. Most participants were able to cope with this test situation and fulfilled the criteria for a technically satisfactory maximum test.

12.1.4 Reference values

The "ATS/ACCP Statement on Cardiopulmonary Exercise testing" from 2003 (238) states that the choice of reference equation is difficult, as none of those published were considered optimal.

In the present study, groups of different ages were assessed. For children and adolescents we chose to follow the advice given in Table 14 of the "ATS/ACCP Statement", which points at Jones et al. from 1985 (247). This data-set is based on cycle ergometer, and in the context of treadmill exercise the applied equations most certainly provide predicted values that are too low. As this was a controlled study, this weakness was considered unimportant for group differences. However, this choice of reference equation probably explains why mean exercise capacity exceeded 100% predicted for most study groups in papers #1 and #3.

A new set of reference equations for adults based on treadmill exercise in a large sample of Norwegian subjects older than 20 years of age were published in 2013 (153). We therefore used these equations to calculated predicted values for the adult part of the cohort in paper #2. As a group, those born EP had results which were considered to be in a normal range.

12.1.5 Statistical power

The size of the groups that were studied in the present thesis is comparable to the size of the groups that have been studied in other reports on exercise outcomes in preterm-born individuals (178, 181, 184, 185). In retrospect and given the observed distribution of peak$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$), our first follow-up had 80% power to detect a difference of 4.0 ($mL \cdot kg^{-1} \cdot min^{-1}$) between the EP and term-born group in both birth-cohorts. At second follow-up, the study had 80.4% power to detect a group difference of 4.0 ($mL \cdot kg^{-1} \cdot min^{-1}$) in 1982-85 cohort, and 94% power to detect a group difference of 3.0 ($mL \cdot kg^{-1} \cdot min^{-1}$) in the 1991-92 cohort, providing a 5% significance level.

The differences for the main outcome variables that were in fact observed between the EP-born and term-born groups were approximately 10%, or for peak$\dot{V}O_2$ approximately 4 ($mL \cdot kg^{-1} \cdot min^{-1}$), which is in the range of the detection limits of the study as given by the power calculations. In paper #1 and #2 these differences were marginally significant, whereas in the paper #3 relatively similar differences were significant. However, in all three papers the data-sets point in the same direction and the difference becomes clearer at the second follow-up.

Paired analyses were used between groups that were paired, i.e. in cross-sectional analyses of complete EP-born vs. term-born groups and in the longitudinal analyses. In paper #1 we used paired Student's t-tests whereas in the remaining papers we used the mixed linear models provided by SPSS (MLM) because the MLM allows for contribution from pairs that are "uneven" due to drop-outs in the statistical models. By nature paired analyses increase the statistical power of the analyses, a factor of particular importance in medium-sized data-sets like the present.

12.2 Discussion of results

Compared to matched controls born at term, survivors of extreme preterm birth had on average an approximately 10% reduced exercise capacity in late childhood and early adulthood. However, the mean values were within levels considered normal. Differences between EP-born and term-born controls were largely explained by differences for the males, but this apparent gender difference did not reach statistical significance when tested with interaction terms. Changes in measures of exercise capacity through puberty from 10 to 18 and from 18 to 25 years of age did not differ from what was observed for term-born controls. Current airway obstruction was unrelated to current measures of exercise capacity in all subgroups of the study. Individuals with a neonatal history of surgical closure of PDA were at high risk of left sided laryngeal paralysis and an associated increased risk of respiratory symptoms and airway obstruction, but without consequences for exercise capacity. There were no strong associations between neonatal factors and later exercise capacity, and in particular a neonatal history of BPD did not influence outcome. There was no association between reported physical activity and peak$\dot{V}O_2$ at 10 years of age, but at the later ages the two variables were significantly and positively associated in both the EP-born and term-born groups in both participating birth cohorts.

12.2.1 Exercise capacity after preterm birth

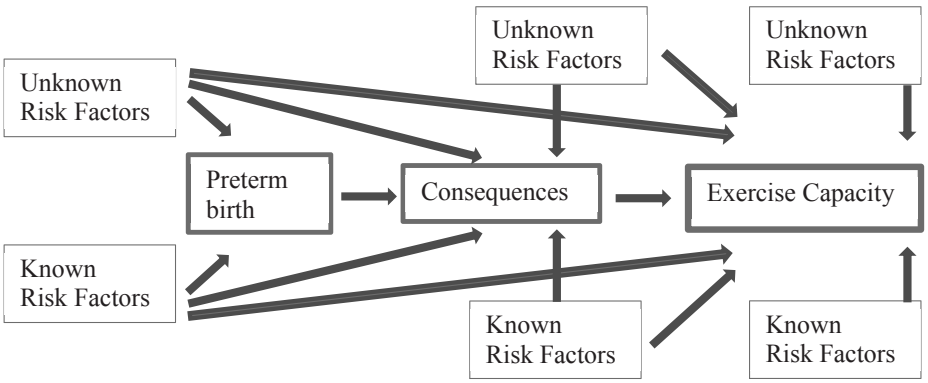
Studies on exercise capacity after extreme preterm birth have generally reported significant differences compared to term-born controls, whereas data from studies on very low birth weight (VLBW) subjects are more diverse; however, in nearly all studies the focus of the discussion has been on why preterm-born subjects seem to have a limited exercise capacity.

Preterm-born individuals constitute a heterogeneous group. The cause of the preterm delivery, immediate perinatal events, complications, injuries and necessary treatments, as well as a variety of subsequent lifestyle factors, could theoretically influence skills,

capabilities, participation and responses to physical training in later life, and thereby negatively influence exercise capacity.

It is highly unlikely that one single causal factor explains reduced exercise capacity in all preterm-born individuals, and if it were, it is also questionable if a study like the present could single it out, given the compound background of this group and the extensive co-linearity between relevant and accessible exposure variables. Moreover, exercise capacity in this context will necessarily be influenced by a range of known and unknown confounding factors that might operate at several levels. The given model (Figure 8) is an attempt to picture some of this complexity.

Figure 8. Possible determinants of exercise capacity



12.2.1.1 Prenatal risk factors

Few prenatal factors could be addressed in this study. However, we had data on smoking during pregnancy and antenatal maternal treatment with corticosteroids, both were unrelated to later exercise capacity. Socio-demographic factors can be related to both preterm birth and exercise capacity. In our study groups, there were no significant differences between the EP and term-born groups regarding educational level of parents, and the groups were too small to explore these issues further.

12.2.1.2 Lung function

Lung function has been related to exercise capacity in several studies (182, 185, 187-189, 192). Most authors have reported that preterm-born subjects with BPD use a greater portion of their ventilatory reserve during exercise, and some have also reporting a decrease in SaO_2. However, only one study (189) has reported a significant reduced peak$\dot{V}O_2$ in subjects with neonatal BPD, and the authors explained their finding as deficits of gas exchange during exercise. The EP-born subjects in our birth cohorts had a 7-10% reduced gas exchange at rest, but it was not associated with the severity of BPD (248). FEV_1% predicted was significantly lower in the EP-born compared to the term-born group, especially in the BPD group (249). Split by BPD, relatively large deficits in lung function became apparent for those with the most severe neonatal respiratory morbidity, particularly regarding FEF_{25-75} but also FEV_1. Setting lower limits of normal (LLN) as suggested by "Global Lung Function Initiative" (250) revealed that *average* FEV_1 was above LLN in the "un-split" EP-born group. Peak$\dot{V}O_2$ appeared unrelated to FEV_1 and was not reduced in subjects within the lower quartile for FEV_1 and it was also unrelated to neonatal BPD. Thus, as judged by our studies, lung function by itself should not represent a limitation to normal exercise performance in this group of EP-born subjects. This observation fits clinical experience from our own department with other chronically ill lung patients, such as cystic fibrosis, where associations between FEV_1 and peak$\dot{V}O_2$ become evident only at relatively severe airway obstruction.

These findings underscore the large reserve capacity of the airway tree at young age, and also suggest that BPD in survivors of more recent years is likely to reflect a different pulmonary "picture" than BPD from the time when it was first described (251). Given the severe abnormalities described in pulmonary autopsy reports from infants who died from BPD, these findings support the notion of continued remodeling of alveolar structures (40). However, to what extent lung function will appear as a limiting factor for ventilation and/or gas exchange during exercise in adulthood, can only be determined by performing even longer longitudinal follow-up studies, at ages when the expected age-related decline has begun to evolve.

12.2.1.3 Infant period - consequences

Extremely preterm birth is usually linked to long periods of variable oxygen treatment, positive pressure ventilation, circulatory instability, and massive use of medication of various kinds. To our knowledge, we still do not fully understand if and to what extent these factors influence the cardiovascular system, peripheral muscles and other organ systems involved in high intensity exercise.

Our study did not find associations between duration of ventilator treatment or neonatal oxygen treatment, or occurrence of postnatal septicemia and later exercise capacity. The only neonatal factor associated with exercise capacity in later life was postnatal treatment with corticosteroids which was negatively associated with treadmill distance both at 10 and at 18 years of age in the 1991-1992 cohort. Postnatal corticosteroids is used to treat chronic lung disease in preterm-born infants and have been negatively associated with later cognitive, motor and coordination skills, and causal relationships have been discussed (252). It has also been proposed that it can induce muscle atrophy (253). It is therefore not unlikely that postnatal corticosteroids may have a direct negative effect on exercise capacity. However, given the design of this study and extensive co-linarites between this treatment and a range of unfavorable conditions, direct causal relations remain speculative.

12.2.1.4 Consequences after PDA ligation

Paper #4 highlights that we should be prepared for hitherto unknown long-term consequences from NICU care. Thirteen participants born EP in 1982-85 had performed surgical ligation of a persistent PDA, and seven of the 11 who underwent laryngoscopy had evidence of left sided laryngeal paralyses. These subjects also had poor FEV_1 and more respiratory symptoms. Interpretation of this finding is challenged by the fact that adverse neonatal events or diseases that can lead to later functional or structural deficits or abnormalities tend to occur in the same infant, rendering these variables co-linear in statistical modelling. Thus, infants who undergo PDA ligation are usually the most immature and sickest of the preterm-born population. The procedure is basically performed in order to facilitate better cardiopulmonary function

in infants who are already ill and to accomplish weaning from positive pressure ventilation. The surgically treated infants are therefore also those who are most likely to develop BPD. However, splitting the group with BPD by presence or absence of LVCP revealed significant differences in FEV_1, a finding that may indicate that LVCP contributes independently to later airway obstruction. Few subjects contributed to these analyses and the finding must be explored in larger studies.

Even if asthma seemed to be similarly distributed between the groups, two subjects with LVCP had a history of difficult to treat asthma and three reduced their medication after being diagnosed with LVCP. One subject had been exposed to extensive examinations in early childhood for "paroxysmal spells". Thus, there is a risk for these individuals to be exposed to unnecessary examinations and to be assigned erroneous diagnoses and treatments.

Surprisingly, the exercise test results did not show any tendency towards lower exercise capacity in subjects with LVCP. When interpreting these results we must bear in mind the small number of participants. In depth investigation of subjects with a history of PDA ligation with subsequent LVCP was not a declared aim of the study, and the data presented should be viewed as an encouragement for further research in this area.

12.2.1.5 Physical activity later in life

Exercise capacity is influenced by the amount and type of exercise invested and by individual trainability. We know that EP birth carries an increased risk for a range of shortcomings that may negatively influence exercise skills as well as participation, such as cognitive, neurological or sensory deficiencies and developmental coordination disorders, all probably increasing the risk of de-training. Reduced participation in physical activities is a major concern related to preterm birth (181, 227-229) although some studies have reported similar level of physical activity compared to peers with normal birth weight (178, 225, 226, 254). Welsh et al. (178) found lower peak$\dot{V}O_2$ but a similar level of physical activity in 11 year old subjects

born EP compared to term-born controls, where physical activity was objectively recorded with accelerometers. This lack of association may be due to the age group studied. Studies have suggested that children born preterm and at term participate equally in physical activity prior to adolescence, but that those born preterm are less active later on (230). In our study-groups there was no association between physical activity and peak$\dot{V}O_2$ at 10 years, but both at 10 years and later the level of physical activity was significantly lower in the EP-born than the term-born controls, except that the difference was only marginally significant at 25 years in the 1982-85 cohort.

Differences in the level of physical activity stand out as a major explanatory factor for reduced peak$\dot{V}O_2$ in the EP-born subjects in our study, and our findings corresponds to those of others (179-181, 185). Physical inactivity due to real or perceived limitations or weaknesses will eventually lead to reduced physical fitness that by itself may reinforce a negative attitude toward exercise and establish negative circles with long-lasting effects. Supporting this line of reasoning, Hallal et al. (225) suggested that early formation of behavioral patterns may be more important than birth weight in predicting later physical activity.

12.3 Why is exercise important in preterm born individuals?

Peak$\dot{V}O_2$ in the EP-born and term-born groups developed similarly from 10 to 25 years of age. In studies of the general population, both peak$\dot{V}O_2$ and FEV_1 exhibit a physiological decrease throughout adulthood. To what extent people born preterm will follow a similar pattern is unknown.

There is some concern that subgroups of individuals born preterm may be more likely to develop COPD and thereby ventilatory insufficiency with consequence for exercise capacity. Interesting in this context is a recent long-term follow-up study indicating that exercise may in fact reduce the physiological age-related decline in FEV_1 (133). Similar to what has been said of a physiological decline in FEV_1 and a potential for later COPD, can be said also for peak$\dot{V}O_2$ and a potential for reaching levels later in life that are associated with morbidity. The HUNT Fitness Study suggested that a

peak$\dot{V}O_2$ (mL·kg^{-1}·min^{-1}) of 44.2 in men and 35.1 in women may represent thresholds of cardiovascular risk (4). In this context a 10% decrease may be of clinical relevance. Preterm-born individuals appear to be more susceptible of life style related diseases such as cardiovascular disease, type 2 diabetes, hypertension and all-cause mortality, as stated previously. Exercise and increased peak$\dot{V}O_2$ reduce risk factors for these conditions, both in the general population and in people with established risk factors for cardiovascular disease (4, 112, 255). Given their highly unusual start in life, we cannot indiscriminately assume similar causal pathways or extrapolate these associations directly to the preterm-born population. There are at least two aspects of relevance; is the increased risk reversible also in preterm-born, and are preterm-born subjects trainable. It has been claimed that preterm-born subjects are non-responders (256), but reports from animal studies have shown that e.g. effects from fetal programming may be reversible in some ways (257-259). Our study suggests that EP-born subjects increase their peak$\dot{V}O_2$ by exercise in the same way as term-born, at least within normal levels of physical activity. There is also reason to believe that exercise may have a positive effect on the increased risk of morbidity. Animal models support, that physical activity can improve risk levels for metabolic disease at least in LBW individuals (260, 261). In addition, there are reports indicating that this may also be true for preterm-born humans (262-264). One study on 9-15 year old preterm-born children did not find any positive effect on risk profiles from physical activity(265), but a lack of effect may be due to the age-group studied. Although final proofs of direct beneficial effects from exercise on cardiovascular risk factors in childhood is missing, it has never been shown to be disadvantageous. Solid data on these issues will require interventional studies with more participants.

12.4 Conclusion

Given the strains and the trauma of being born in the middle of fetal development and spending most of third trimester of pregnancy in a neonatal intensive care unit, we were intrigued by the modest decreases that we observed for exercise capacity in most of the long-term survivors of EP-birth. Moreover, in view of the heterogeneity reported for the response to physical training in the general population (146), we were also intrigued by the positive association between physical activity and peak$\dot{V}O_2$ observed in late adolescence and early adulthood. Similar changes in EP and term-born participants from mid-childhood to early adulthood for measures of exercise capacity are certainly encouraging. There were few indications that particular neonatal factors influenced the exercise outcomes, notably also that neonatal BPD did not appear to have a significant negative impact. Importantly, current FEV_1 did not seem to limit exercise capacity, not even in those with FEV_1 in the lowest quartile. The overall findings were therefore promising, but to understand causal pathways and to fully conclude on long-term health protective effects from physical activity in EP-born individuals as compared to that of the general population, will require larger and preferably interventional studies.

13. LIMITATIONS

An observational study design cannot provide hard data explaining cause and effect with certainty, but only point at associations between the explored exposure and outcome variables. Although comparable to most other research performed in this area, our two birth-cohorts were relatively small. Subgroup analyses involving gender and stratification on neonatal BPD revealed associations that can be of interest for the understanding of causal relationships. However, low statistical power requires cautious interpretations, and solid knowledge will require larger number of participants. Physical activity was assessed using questionnaires, and data would have been more verifiable had e.g. diaries or accelerometers been used. The findings of left-sided laryngeal paralysis after neonatal PDA surgery could reflect local circumstances, and needs to be reproduced in other cohorts treated at other hospitals.

14. GENERAL CONCLUSION

- Exercise capacity was on average 10% lower in the EP-born group compared to the term-born control group; however, still within what is considered a normal range in most participants. *$H0_1$ rejected in most of the analyses.*
- EP-born subjects and term-born subjects share the same pattern of development in exercise capacity from 10 to 18 years of age and 18 to 25 years of age.
  $H0_2$ and $H0_3$ sustained.
- FEV_1 was significantly lower in EP-born subjects, but unrelated to measures of exercise capacity. *$H0_4$ sustained*.
- BPD was unrelated to measures of exercise capacity. *$H0_5$ sustained.*
- EP-born children with a history of neonatal surgery for PDA are at risk of left-sided laryngeal dysfunction, but this was not significantly related to exercise capacity. These subjects are at high risk of diagnostic misclassification and should be examined with laryngoscopy if complaining about exercise induced breathing difficulties. *$H0_5$ sustained.*
- Postnatal treatment with dexamethasone was negatively associated with distance completed on the treadmill, especially in the 1991-92 cohort. All other neonatal factors were unrelated to measures of exercise capacity.
  $H0_5$ rejected for postnatal corticosteroids, otherwise sustained.
- Physical activity was positively and similarly associated with exercise capacity in both the EP-born and the term-born subjects at 18 and 25 years of age, but not at 10 years of age. *$H0_6$ rejected, except at age 10.*
- EP-born subjects seem to be less physically active than term-born subjects and should be encouraged to be more physically active from an early stage of life.
  $H0_7$ rejected in most analyses, but not all.

Exercise skills and abilities and the environment in which a child is raised are strong psychosocial determinants for exercise participation. We cannot draw firm conclusion as to whether the modest decreases in exercise capacity in EP-born participants of the present study primarily were related to biological factors or to psychosocial issues.

However, the data support that of most preterm born individuals are able to attain normal levels of exercise capacity, given normal exercise habits. Early formation of exercise habits during childhood and adolescence can be an important and modifiable factor that can influence later exercise capacity also in these vulnerable individuals.

15. PERSPECTIVE

There is good evidence that exercise promotes health; however, more research needs to be done in subgroups with higher risks of later diseases, such as preterm-born children. Interaction effects between being born preterm, physical activity, physical training, exercise capacity and future disease remain to be explored. To this end, we need objective measurements of habitual physical activity and long-term follow-up at regular intervals over decades, and preferably also controlled intervention trials.

15.1 Follow-up on those who had surgical PDA closure

Left vocal fold paralysis in a majority of adults with neonatal PDA surgery, signals that these individuals need better follow-up. Laryngoscopy should be done at least in subjects with respiratory symptoms in order to make a correct diagnosis and to avoid unnecessary diagnostic workup and treatments. To what extent our findings can be reproduced in other groups of preterm-born subjects need to be explored. This research is now under construction in a national group of 52 subjects born EP during 1999-2000 with neonatal surgical closure of the PDA performed in different hospitals.

15.2 Further research

Tracking of exercise capacity further into adulthood should be addressed with focus on relationships and interaction effects between preterm birth, physical activity, physical training, trainability, exercise capacity and future disease. Preferably, studies applying interventional designs should also be included. If exercise proves to have similar health protective effects in preterm-born as has been established for the general population, this potentially modifiable trait should be exploited to the benefit of this new and vulnerable group of fellow citizens.

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