DISSERTATION FROM THE
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Mari Bratteteig

Physical activity, fitness, and cardiovascular disease risk in childhood cancer survivors:

The Physical Activity in Childhood Cancer Survivors (PACCS) study

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Sammendrag

Bakgrunn: Barnekreftoverlevere har økt risiko for seneffekter fra kreftbehandling. Fysisk aktivitet kan potensielt modifisere risikoen for vanlige seneffekter, som kardiovaskulær sykdom (CVD). Det mangler kunnskap om nivået av fysisk aktivitet, basert på robuste målemetoder, i store utvalg av unge overlevere. Videre vet vi lite om risikofaktorer for CVD manifesterer seg allerede i ungdomstiden, og om sammenhengen mellom fysisk aktivitet, fysisk form og risikofaktorer for CVD.

Mål: Hovedmålene med denne avhandlinger var **I)** å beskrive nivåer av fysisk aktivitet og sedat tid blant unge barnekreftoverlevere, og å sammenligne nivåer av fysisk aktivitet og sedat tid med alder- og kjønnsstratifiserte referanser; **II-III)** å sammenligne risikofaktorer for CVD hos unge overlevere med alder- og kjønnsstratifiserte referanser og kontroller, og å undersøke sammenhengen mellom fysisk aktivitet og ulike domener av fysisk form med risikofaktorer for CVD hos overlevere og kontroller.

Design og deltakere: Denne avhandlingen er basert på tverrsnittsdata fra arbeidspakke 1 og 2 i den internasjonale, multisenterstudien *Physical Activity in Childhood Cancer Survivors (PACCS)*. Deltakere i alderen 9-16 år med en hvilken som helst tidligere kreftdiagnose, som hadde gjennomført kreftbehandling ≥ 1 år tidligere, var kvalifisert til å delta i den første arbeidspakken. Deltakere 9-18 år, som var i stand til å utføre en kardiopulmonær arbeidsbelastningstest, ble videre invitert til å delta i arbeidspakke 2.

Metode: Individuelle CVD risikofaktorer ble vurdert basert på kardiorespiratorisk form (kun i Paper II), grad av fedme (kroppsmasseindeks (KMI) eller android fettmasse), systolisk blodtrykk (SBT), ratio av total-kolesterol og HDL-kolesterol (Total/HDL), og langtidsblodsukker (HbA1c, kun i Paper III). I tillegg kalkulerte vi gjennomsnittet av standardiserte skårer (z-skårer) for kardiorespiratorisk form, KMI, SBT og Total/HDL for å lage en CVD risikoskår (Paper II). Fysisk aktivitet og sedat tid ble vurdert med akselerometre, kardiorespiratorisk form med kardiopulmonær belastningstest, og muskelstyrke med maksimale isometriske styrketester.

Hovedresultater: **I)** Blant unge barnekreftoverlevere (gjennomsnittsalder 12,2 år) var det 34% som var fysisk aktive i gjennomsnitt ≥ 60 minutter hver dag. Risikofaktorer for lavere fysisk aktivitet og/eller høyere sedat tid var å være jente, eldre, overvektig, overlever av CNS tumor, og ha hatt tilbakefall av kreft. Generelt var gutteoverleverne mindre fysisk aktive

sammenlignet med referansene, mens jenteoverleverne var lik referansene. Både gutte- og jenteoverleverne tilbrakte mer tid sedat. **II-III)** Angående risikofaktorer for CVD hadde gutteoverleverne lavere kardiorespiratorisk form sammenlignet med referansene, men lik KMI, SBT og Total/HDL. Jenteoverleverne og referansene hadde like nivåer av alle risikofaktorene for CVD. Sammenlignet med kontrollene hadde overleverne mer android fettmasse og lavere SBT, mens Total/HDL og HbA1c var likt. Mer tid i fysisk aktivitet av alle intensiteter var assosiert med høyere kardiorespiratorisk form, og mer tid i fysisk aktivitet av moderat og hard intensitet var i tillegg assosiert med lavere Total/HDL, og en lavere CVD risikoskår. Mer tid i moderat-til-hard fysisk aktivitet, høyere kardiorespiratorisk form og muskelstyrke var assosiert med lavere nivåer av android fettmasse og Total/HDL, og med høyere SBT blant overleverne. Verken moderat-til-hard fysisk aktivitet, kardiorespiratorisk form eller muskelstyrke var assosiert med HbA1c. Sammenehengene mellom kardiorespiratorisk form og muskelstyrke med android fettmasse var sterkere hos overleverne sammenlignet med kontroller.

Konklusjon: Samlet sett hadde unge barnekreftoverlevere ugunstige nivåer av fysisk aktivitet, sedat tid, og noen risikofaktorer for CVD. Blant overleverne var mer tid i høyere intensiteter av fysisk aktivitet, sammen med høyere kardiorespiratorisk form og muskelstyrke, assosiert med gunstigere nivåer av risikofaktorer for CVD. Ettersom ungdomsstiden er en avgjørende tidsperiode med hensyn til etablering av livsstilsvaner, etterlyser vi skreddersydde intervensjoner for å øke fysisk aktivitet og redusere sedat tid blant unge overlevere, og for å undersøke effekten på CVD risikofaktorer, i longitudinelle studiedesign.

Nøkkelord: Barnekreftoverlevere, fysisk aktivitet, sedat tid, akselerometri, kardiorespiratorisk form, muskelstyrke, risiko kardiovaskulær sykdom

Summary

Background: Childhood cancer survivors face an increased risk of late effects from cancer treatment. Physical activity may modify the risk of common late effects, such as cardiovascular disease (CVD). Evidence concerning levels of physical activity in large samples of adolescent survivors based on robust measurement methods is lacking. Moreover, whether CVD risk factors are present already in adolescence and how physical activity and fitness are associated with CVD risk in this population is not well studied.

Aims: The main aims of this thesis were **I)** to describe levels of physical activity and sedentary time in young childhood cancer survivors and to compare levels of physical activity and sedentary time with age- and sex-stratified references, **II-III)** to compare CVD risk factors in young survivors with age- and sex-stratified references and controls and to examine the associations between physical activity and different domains of fitness with CVD risk factors in survivors and controls.

Design and participants: This thesis was based on cross-sectional data from work packages 1 and 2 of the international, multicenter *Physical Activity in Childhood Cancer Survivors (PACCS)* study. Participants aged 9-16 years with any previous cancer diagnosis who had completed cancer treatment ≥ 1 year ago were eligible to participate in the first work package. Participants from 9-18 years who were able to perform a cardiopulmonary exercise test were further invited to work package 2.

Methods: Single CVD risk factors were assessed based on cardiorespiratory fitness (Paper II only), adiposity (body mass index (BMI) or android fat mass), systolic blood pressure (SBP), ratio of total-cholesterol to HDL-cholesterol (Total/HDL), and glycosylated hemoglobin (HbA1c, Paper III only). Additionally, standardized scores (z-scores) of cardiorespiratory fitness, BMI, SBP, and Total/HDL were averaged to create a CVD risk score (Paper II). Physical activity and sedentary time were assessed by accelerometry, cardiorespiratory fitness by cardiopulmonary exercise test, and musculoskeletal fitness by maximal isometric strength tests.

Main results: **I)** Among young childhood cancer survivors (mean age 12.2 years), 34% were physically active for ≥ 60 minutes per day on average. Risk factors of lower physical activity and/or higher sedentary time were being female, older, overweight, a survivor of CNS tumor, and having experienced a relapse. In general, male survivors were less physically active

compared to the references, whereas female survivors were similar to the references. Both male and female survivors spent more time sedentary than the references. **II-III)** Concerning CVD risk factors, male survivors had lower cardiorespiratory fitness compared to the references but similar BMI, SBP, and Total/HDL. Female survivors and the references had similar levels of all the CVD risk factors. Compared to the controls, survivors had higher levels of android fat mass and lower SBP, whereas Total/HDL and HbA1c were similar. Spending more time in all intensities of physical activity was associated with higher cardiorespiratory fitness, while more time in moderate and vigorous intensities were additionally associated with lower Total/HDL and a lower CVD risk score. More time in moderate-to-vigorous physical activity, higher cardiorespiratory, and higher musculoskeletal fitness were associated with lower levels of android fat mass and Total/HDL and higher SBP in survivors. Neither moderate-to-vigorous physical activity, cardiorespiratory fitness, nor musculoskeletal fitness were associated with HbA1c. The associations between cardiorespiratory and musculoskeletal fitness with android fat mass were stronger in survivors compared to the controls.

Conclusion: Overall, young childhood cancer survivors had unfavorable levels of physical activity, sedentary time, and some CVD risk factors. Among survivors, spending more time in higher intensities of physical activity, together with higher cardiorespiratory and musculoskeletal fitness, were associated with more favorable levels of CVD risk factors. As adolescence is a crucial period with respect to establishing lifestyle habits, we call for tailored interventions to increase physical activity and reduce sedentary time in young survivors and to examine the effect on CVD risk factors in longitudinal study designs.

Keywords: childhood cancer survivors, physical activity, sedentary time, accelerometry, cardiorespiratory fitness, musculoskeletal fitness, cardiovascular disease risk

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Mari Bratteteig,
Mai 2023, Oslo

List of papers

This dissertation is based on the following original research papers, which are referred to in the text by their Roman numerals:

I. Grydeland M*, Bratteteig M*, Rueegg CS, Lie HC, Thorsen L, Larsen EH, Brügmann-Pieper S, Torsvik IK, Götte M, Lähteenmäki PM, Kriemler S, Fridh MK, Anderssen SA, Ruud E. *Device-measured physical activity in adolescent childhood cancer survivors: the PACCS study.* [Manuscript revised and re-submitted to *Pediatrics]*

II. Bratteteig M, Anderssen SA, Rueegg CS, Ruud E, Torsvik IK, Kriemler S, Grydeland M (2022). *Device-measured physical activity and cardiovascular disease risk in adolescent childhood cancer survivors. A physical activity in childhood cancer survivors (PACCS) study.* Frontiers in Pediatrics. doi: 10.3389/fped.2022.977365.

III. Bratteteig M, Rueegg CS, Raastad T, Grydeland T, Torsvik IK, Ruud E, Anderssen SA. *Physical activity, fitness, and cardiovascular disease risk in adolescent childhood cancer survivors compared to controls. The physical activity in childhood cancer survivors (PACCS) study.* [Manuscript submitted to *Journal of Adolescent and Young Adult Oncology*]

Abbreviations

ALL	Acute lymphoblastic leukemia
BMI	Body Mass Index (kg/m^2)
BP	Blood pressure
CCS	Childhood cancer survivors
CNS	Central nervous system
CPET	Cardiopulmonary exercise test
CPM	Counts per minute
CRF	Cardiorespiratory fitness
CVD	Cardiovascular disease
DXA	Dual-energy X-ray absorptiometry
FFM	Fat-free mass
FM	Fat mass
HbA1c	Glycosylated hemoglobin
LPA	Light-intensity physical activity
LRT	Likelihood-ratio test: Assessment of goodness-of-fit in two competing statistical models
MPA	Moderate-intensity physical activity
MSF	Musculoskeletal fitness
MVPA	Moderate-to-vigorous-intensity physical activity
PA	Physical activity
PACCS	Physical Activity in Childhood Cancer Survivors
SBP	Systolic blood pressure
ST	Sedentary time
Total/HDL	Ratio of total-cholesterol to high-density lipoprotein-cholesterol
$VO_{2\text{-peak}}$	Peak oxygen consumption
VPA	Vigorous-intensity physical activity
WP	Work package

Term clarifications

As there is a limited body of knowledge concerning adolescent childhood cancer survivors, studies reflecting age spans other than adolescence will also be referred to if necessary. Below are clarifications of terms that are frequently used throughout this thesis

Childhood cancer survivors refer to survivors of cancer that were diagnosed < 20 years of age.[1]

Young childhood cancer survivors refer to both children (< 10 years of age) and adolescents (≥ 10 and < 20 years of age).

Adolescent childhood cancer survivors refer to adolescents only (≥10 years and < 20 years) or when the mean age of the sample lies within the adolescent age span.

Young adult childhood cancer survivors refer to young adults only (≥ 20 and < 40 years of age) or when the mean age of the sample lies within the young adult age span.

List of tables and figures

Table of Contents

1.0 Introduction

From the beginning of the 20th century, the discoveries of radiotherapy (~1900), chemotherapies (~1950), and bone marrow transplantation (~1970), together with new diagnostic methods (~1970) and supportive care, have drastically improved survival rates for cancer.[2,3] For example, in Norway, overall survival rates increased from about 30% to > 75% in the period from 1965-2020.[4]

However, cancer still constitutes a major societal burden that impacts families and has a high cost for our health and social systems.[5] Notably, cancer is the leading cause of death in Norway,[6] and the mortality rate is fairly stable or only slowly in decline.[4] The discrepancy between the relatively high increase in survival rate and a relatively slow decline in mortality rate is due to the rapid increase in cancer incidence.[7] Increased incidence and survival rates have led to an increasing population of cancer survivors, however, at risk of treatment-induced late effects. Subsequently, attention towards harmful late effects of cancer treatment is growing, and modern cancer treatment has shifted from pure survival to long-term health and improved quality of life.[8,9]

Reducing treatment intensity or changing treatment protocols have been strategies to reduce late effects among cancer survivors (primary prevention of late effects). One such example is the treatment of Hodgkin's lymphoma patients, where changing chemotherapeutic drugs and limiting radiation fields with lower doses led to reductions in the risk of life-threatening diseases, such as secondary cancer and cardiac disease.[10] Other means suggested to reduce late effects from cancer are lifestyle modifications, such as eating a healthy diet, maintaining a healthy body weight, and being physically active (secondary prevention of late effects).[11] In survivors of adult-onset cancer, lifestyle modifications have been successful in terms of achieving better physical, mental, and social functioning and a higher level of well-being.[12-14] Less is known about survivors of childhood cancer.[15,16]

This thesis will focus on childhood cancer survivors (CCS), physical activity (PA), fitness, and cardiovascular disease (CVD) risk. In the following introductory sections, a description of childhood cancer, its treatments, and potential late effects from treatment will be given. Cardiovascular disease is highlighted as an important late effect. Relevant literature on PA and fitness among CCS, and how PA and fitness may play important roles in the secondary prevention of CVD is addressed, to situate the need for new knowledge, and to justify the aims of this thesis, which are described at the end of the introductory sections.

1.1 Childhood cancer

Incidence, diagnosis, and prognosis

In Norway, childhood cancer accounts for about 0.6% of all cancer cases,[4] with approximately 200 children and adolescents being diagnosed with cancer each year.[17] Childhood cancer is the leading cause of death in children aged 1-17 years in this country,[6] and the incidence is highest in the age groups from 0-4 years and 13-17 years.[17]

Childhood cancer is heterogeneous with more than 100 entities.[18] The three most common diagnostic groups of cancer in children are tumors in the central nervous system (CNS), which account for ~28% of all childhood cancers, followed by leukemias and lymphomas (Figure 1).[19] Next to lymphatic tissue proliferation in early childhood is the growth rate of the brain, suggesting that normal growth processes contribute to tumor development.[20] The most frequent CNS tumors are astrocytoma and medulloblastoma tumors, which are predominantly situated in the brainstem and cerebellum, respectively.

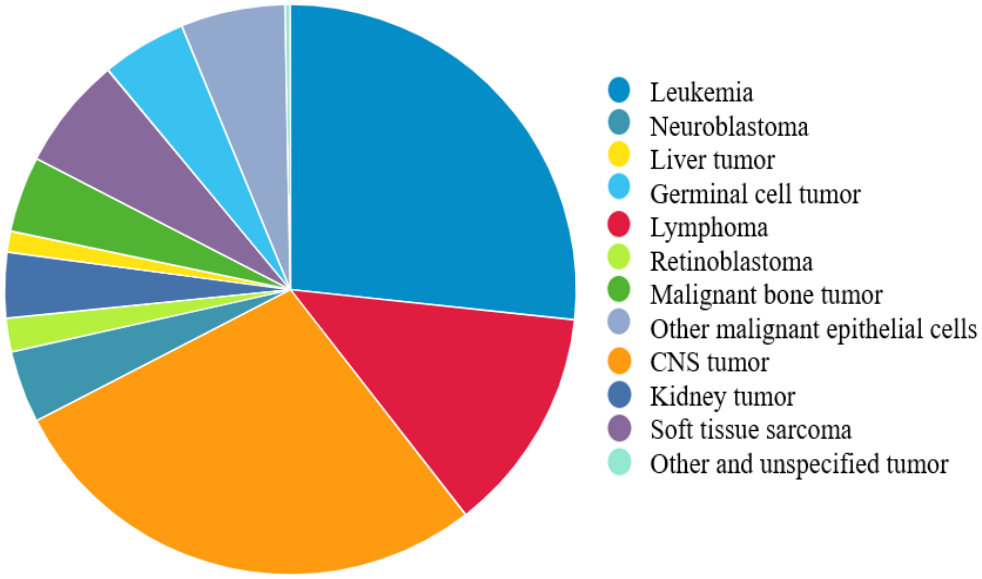

Figure 1: Distribution of childhood cancer diagnostic groups in Norway from 2003-2021. Published with permission from the Cancer Registry of Norway and Kreftlex.[17,19]

Leukemia is a collective term for hematological cancers affecting the blood cells,[21] and accounts for ~27% of all childhood cancers.[19] With leukemias, there is an overproduction of non-functioning immature white blood cells (blasts) in the bone marrow, which "crowd out" useful cells. In children, acute lymphoblastic leukemia (ALL) is the most common type of

leukemia, followed by acute myeloblastic leukemia.[22,23] Among children aged 1-6, ALL is more common, whereas the incidence of acute myeloblastic leukemia is similar during childhood and adolescence.

Lymphoma is a collective term for cancer types that affect lymphocytes (B- and T-lymphocytes) and accounts for about 13% of all childhood cancers.[19] The two main groups are Hodgkin's lymphoma and non-Hodgkin's lymphoma, where the main difference is the type of lymphocytes affected.[24,25] Hodgkin's lymphoma is more common in adolescents and young adults aged 15-30 years, whereas non-Hodgkin lymphoma is more common in children aged 5-10 years.

Historically, the prognosis of childhood cancer has been poor, especially for leukemias (Figure 2). Today, more than 80% of children become long-term survivors (≥ 5 years).[26] In Norway in 2021, there were more than 6000 CCS.[17]

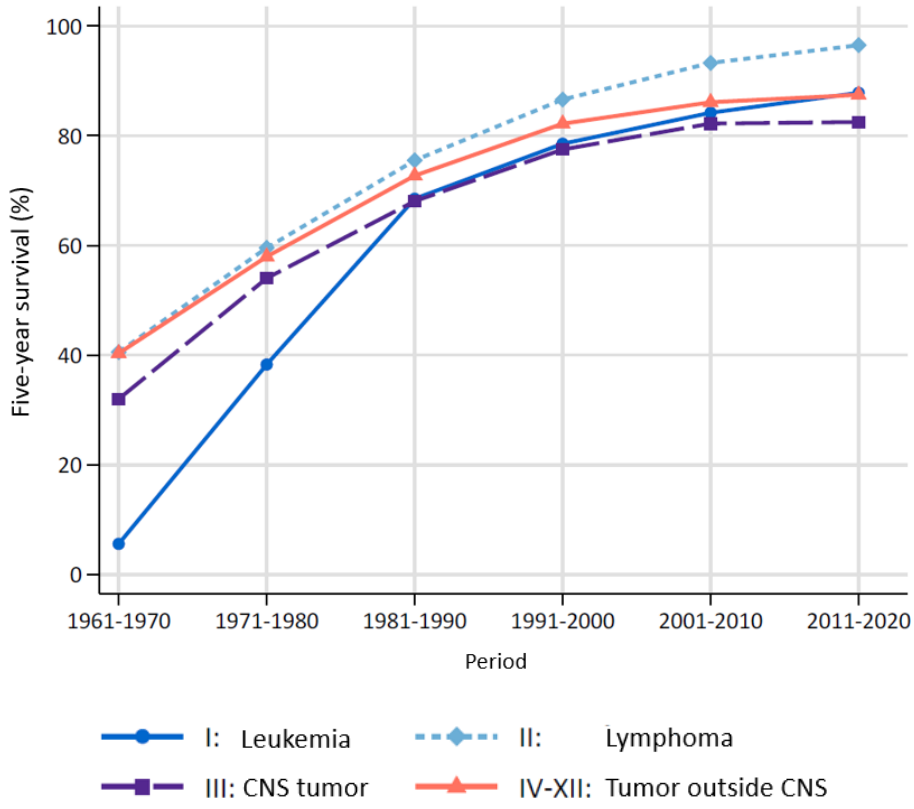

Figure 2: Five-year survival from 1961-2020 in Norway for children and adolescents, stratified by diagnostic group. Published with permission from the Cancer Registry of Norway.[17]

1.2 Cancer treatment

Most often, childhood cancer is treated with different treatment modalities. For example, ALL protocols consist of several types of chemotherapeutic drugs, sometimes in combination with steroids, and in high-risk patients, CNS irradiation and/or hematopoietic stem cell transplantation may become necessary.[22] In researching survivors of adult-onset cancer, it is common to differentiate survivors according to treatment intensity based on the number of treatment modalities received (e.g., for prostate cancer, treatment with surgery only, or surgery + chemotherapy[27]). As treatment of childhood cancer is characterized by multiple modalities with large variations in intensities, it is hard to generalize treatment intensity based on the number of treatment modalities alone in this population.[28]

Surgery

Before the 1950s, surgery constituted the primary modality in the treatment of childhood cancer (solid tumors), with survival rates in the 20% range.[29] Today, surgery is often combined with other modalities, drastically improving survival rates. However, surgery alone is sufficient in some cases, depending on tumor histology and the stage of the disease.

Radiotherapy

Radiotherapy is one of the key treatment components of some childhood cancers, such as CNS tumors and sarcomas, and the main aim is to improve local control.[30] There are different types of radiotherapy, such as conventional megavoltage photon radiotherapy, where energy is attenuated exponentially through the beam/tissue; intensity-modulated radiotherapy, where energy intensity varies in different parts of the beam; and proton beam radiotherapy, where most energy is deposited towards the end of the beam. Radiation is often limited to a certain area, such as the cranium, chest, or pelvis. However, as a preparative regime for hematopoietic stem cell transplantation, total body irradiation is sometimes necessary.

Chemotherapy

Chemotherapy is a cornerstone in the treatment of all childhood hematological cancers, particularly leukemias and lymphomas.[31] Moreover, chemotherapy is often used as a pre-operative treatment to achieve regression in solid tumors or to further facilitate local control through surgery and/or radiotherapy. Chemotherapy can also be used post-operatively when one suspects microscopic metastasis or after incomplete tumor resection therapy. There are a range of different chemotherapies with different qualities, and it is common to combine them to achieve synergetic effects and to avoid chemotherapy resistance.

Hematopoietic stem cell transplant

There are two types of hematopoietic stem cell transplantation: allogeneic and autologous. In allogeneic hematopoietic stem cell transplantation, stem cells from a matched donor are used to replace sick hematopoietic stem cells and to induce an inflammatory process that can cure "sleepy" cancer cells elsewhere in the body (graft-versus-Leukemia).[32] Potential problems include too much inflammation and graft-versus-host-disease that can evolve and increase morbidity.

Autologous hematopoietic stem cell transplantation is used in the treatment of solid tumors that require very strong chemotherapeutic drugs that can result in fatal complications, thereby requiring doctors to refill the patient's stem cells from the stem cell bank to reduce toxic development.[32] The patient's stem cells are harvested in a calm phase before the strong drugs are administered.

1.3 Late effects of cancer treatment

A challenge concerning cancer treatment is the balance between administering "enough" treatment to cure the disease while at the same time reducing the risk of late effects from treatment (what is the "cost of cure"?).[30] Surgery and radiotherapy typically affect the area of exposure, whereas chemotherapeutic drugs and hematopoietic stem cell transplantation may affect the entire body. The combination of treatment modalities has improved survival rates drastically; however, this comes at the cost of increased risk of late effects.[20]

It is important to distinguish between side effects, long-term effects, and late effects from treatment.[33] Side effects refer to unwanted events or troubles lasting from days to weeks (e.g., nausea, hair loss) as a result of treatment, long-term effects refer to events or troubles that arise during treatment and persist (e.g., fatigue, pain), and late effects refer to events or troubles that develop from months to years after treatment ends (e.g., secondary cancer, heart failure). Among children and adolescents, late effects are of particular concern because of their growing and developing bodies[34,35] and long life expectancy after treatment completion.

The longitudinal multi-institutional *Childhood Cancer Survivors Study* from North America reflects the most comprehensive body of information assembled on long-term CCS.[36] Studies published in the early 2000s on childhood cancer cohorts diagnosed and treated between 1970-1986 reported increased mortality,[37] impaired health status,[38] and increased morbidity[39] compared to references or controls. Mertens et al. (2001) observed that the age- and sex-

standardized mortality rate was 10.8 times higher in CCS (n = 20,227) compared to population-based references.[37] Overall, the cumulative mortality rate was 14% 25 years after diagnosis. Recurrence of the original cancer was the leading cause of death (67% of excess deaths), followed by health-related causes other than recurrence (28% of excess deaths). Of these health-related causes of death, excess mortality rates were especially high due to secondary cancers (19.4 times higher risk), pulmonary causes (9.2 times higher risk), and cardiac causes (8.2 times higher risk). Hudson et al. (2003) found that, compared to sibling controls, young adult CCS (n = 9535) were 2-5 times more likely to report adverse general and mental health, activity limitations, and functional impairments.[38] Oeffinger et al. (2006) estimated the cumulative prevalence of self-reported chronic health conditions in young adult CCS (n = 10,397) 30 years after diagnosis to be 73%, and 42% for severe, disabling, or fatal conditions.[39] Compared to sibling controls, common severe or fatal health conditions among CCS include major joint replacement (54-fold increased risk), congestive heart failure (15-fold increased risk), secondary cancer (15-fold increased risk), severe cognitive dysfunction (10-fold increased risk), and coronary artery disease (10-fold increased risk).

Research from the *Childhood Cancer Survivor Study*, which also includes cohorts treated in more recent times, shows similar risk of mortality and morbidity.[40,41] Armstrong et al. (2009) assessed cohorts of CCS diagnosed and treated in the period from 1979-2002 (n = 20,483) and reported a cumulative mortality rate of 18% 30 years after diagnosis.[40] However, they found that the cause of death pattern had changed over time: mortality attributable to recurrence of primary cancer had decreased (58% of excess death), whereas mortality attributable to health-related causes other than recurrence had increased (35% of excess death). Suh et al. (2020) assessed adult cohorts of CCS diagnosed with cancer between the ages of 15-20 years and who were treated in the period from 1970-1999 (n = 5804) concerning both mortality and self-reported chronic health conditions.[41] They reported a cumulative mortality rate of 16% 30 years after diagnosis, and health-related causes other than recurrence were the leading cause of death (52% of excess death), followed by recurrence (36% of excess deaths). Concerning chronic health conditions, the estimated cumulative prevalence 30 years after diagnosis was 75%, and 40% for severe or fatal health conditions. Hudson et al. (2013) clinically ascertained adult CCS (n = 1713) and reported a higher prevalence of chronic health conditions. The estimated cumulative prevalence of a chronic health condition 35 years after diagnosis was 94%, and 75% for a serious, life-threatening, or disabling chronic condition.

1.4 Cardiovascular disease risk in childhood cancer survivors

Cardiovascular diseases are highlighted as serious late effects among CCS.[42] In the studies by Suh et al. (2020) and Armstrong et al. (2009), CCS (30 years from diagnosis) had an almost six-fold increased risk of having a chronic, severe, or fatal cardiac condition compared to their sibling controls,[41] and a seven-fold increased risk of dying from cardiac causes compared to their age- and sex-matched cohorts.[40]

As CVDs are conditions that develop over a long period of time, we usually do not observe CVD in adolescents. However, we try to indicate early damage or predict future CVD risk by looking at indices such as cardiorespiratory fitness (CRF), weight status/body composition, and levels of blood pressure (BP), cholesterol, and glucose/insulin.[43] Collectively, we often term these indices as CVD risk factors or (cardio)metabolic risk factors. In this thesis, the term CVD risk factors will be used.

In 1996, Talvensaari et al. demonstrated that CCS aged 10-31 years (n = 50) had more unfavorable levels of body composition, glucose/insulin, and cholesterol compared to age- and sex-matched controls. Moreover, 16% of CCS, but none of the controls, had a combination of obesity, hyperinsulinemia, and low HDL-cholesterol (metabolic syndrome). Subsequent studies have confirmed that there is an increased prevalence of both single and clustered CVD risk factors in CCS.[44-51] Notably, few of these studies assessed adolescent CCS only.[48,49] According to National Cholesterol Education Program III criteria, Sohn et al. (2011) found a 19% prevalence of metabolic syndrome in a Korean sample of adolescent CCS with mixed cancer diagnoses (n = 98, mean age 11.2 years) and > 60% presented with at least one CVD risk factor.[48] Using the same criteria to define metabolic syndrome, Aldafiri et al. (2012) found a prevalence of 5% among Saudi-Arabian adolescent CCS with standard risk ALL (n = 56, mean age 13.4 years).[49] Almost 40% of the participants presented with one metabolic syndrome component, and > 10% presented with two components.

Whether CVD risk factors are present already in adolescence in European CCS is yet to be explored. Furthermore, a methodological issue in the research of CVD risk is the dichotomization of CVD risk factors according to certain cut-off values that determine whether one is considered to present a CVD risk factor of interest.[52,53] As CVD risk factors develop in continuums, dichotomization of CVD risk factors leads to loss of information. Misclassification may occur, and it may be less reliable to detect risk of CVD into adulthood.[54]

Long-term effects influencing CVD risk factors

Some of the long-term effects that influence CVD risk, such as damage to endocrine structures, are non-modifiable and may require medical treatment.[55] Other long-term effects influencing CVD risk, such as muscular atrophy, unfavorable body composition, reduced fitness, and atherosclerosis, are modifiable by lifestyle behaviors such as PA.[56-58] Moreover, PA can contribute to reducing CVD risk through other pathways outside of the affected organ. For example, if high BP (hypertension) is a consequence of non-modifiable renal dysfunction, PA may lower BP by inducing the release of nitrogen oxide, which has a vasodilatory effect.[59] Below are some examples of long-term effects from cancer treatment that may increase CCS' susceptibility of CVD.

Brain surgery and cranial radiation may cause damage to the pituitary and hypothalamus glands, leading to a deficiency of growth hormone, which is associated with reduced growth, obesity, dyslipidemia, and insulin resistance.[30,60] Damage to this area can also disrupt the hypothalamic appetite-regulating center. Nephrectomy (removal of kidney) is associated with an increased risk of impaired renal function and hypertension.[61]

Irradiation of the thyroid gland increases the risk of hypothyroidism, which is associated with obesity.[62] Irradiation of the heart may lead to cardiac toxicity affecting the valves and coronary arteries.[30] Abdominal irradiation increases the risk of renal late effects, such as chronic renal failure and hypertension. Total body radiotherapy may cause damage to one or more organs, which is associated with insulin resistance, dyslipidemia, and hypertension.

Chemotherapy may cause systemic inflammation, which damages adipose tissue, resulting in adipocyte dysfunction and decreased adipocytokine secretion.[60] Adipocytokines (e.g., leptin and adiponectin) are involved in regulating endothelial function, atherogenesis, and energy balance.[63] Some chemotherapies may also affect energy balance by impacting the constitution of the microbiota or by decreasing gut motility with increased caloric absorption.[60]

Low levels of PA are common during cancer treatment due to factors such as fatigue or fear of injury,[64] with subsequent loss of muscle mass, which in turn decreases glucose uptake in muscle tissue.[62] Reduced energy expenditure can also increase the risk of developing obesity. Being an attribute of PA, CRF is subsequently reduced by low levels of PA, which is associated with insulin resistance, and hence glucose uptake.[65] Low insulin sensitivity may further result in excess release of lipids, mainly from visceral adipose tissue, resulting in elevated levels of triglycerides and increased clearance of HDL-c.

1.5 Physical activity and fitness in childhood cancer survivors

The literature shows that young CCS (children and adolescents) have lower levels of PA,[66] CRF,[67] and musculoskeletal fitness (MSF)[68] compared to controls, which persists many years after treatment completion and may further exacerbate the risk of late effects. The first meta-analysis comparing levels of PA in young CCS to controls was published by Antwi et al. (2019), showing lower PA levels in CCS (Hedges' g = -0.889).[66] However, seven of eight studies included in the meta-analysis assessed PA using subjective measurement methods. The eighth study assessed total PA as total daily energy expenditure, estimated based on individual flex heart rate ("the heart rate which defines the difference between rest and exercise"), and found lower total PA in CCS (n = 88, age range 7-18 years) compared to sibling controls.[69] The few intervention studies that have assessed moderate-to-vigorous-intensity PA (MVPA) in adolescent CCS using accelerometers showed divergent findings in baseline measurements (26-60 minutes MVPA/day).[70,71] However, these studies were limited by small and selective samples. In young adult survivors of childhood ALL (n = 365, mean age 29 years), device-measured MVPA was lower in CCS who had received cranial radiotherapy compared to the controls (18 vs. 25 min) but similar in those who did not receive cranial radiotherapy (21 vs. 25 min).[72] Equivalent studies of adolescent CCS with large sample sizes using objective measurement methods are lacking. Moreover, the knowledge concerning PA intensities in adolescent CCS is limited. Keats et al. (2006) surveyed adolescent CCS (n = 97, age range 15-20 years) to determine the frequency and intensity of PA sessions before, during, and after cancer treatment (mean 2.7 years from diagnosis).[73] Compared to pre-diagnosis, overall PA frequency dropped during treatment but increased to a similar level as before diagnosis post-treatment. However, PA of moderate and strenuous intensity was lower post-treatment compared to pre-diagnosis, whereas PA of mild intensity increased. We know even less about sedentary time (ST) than PA among adolescent CCS. Some studies have found similar or higher levels of screen time in this population compared to controls;[74,75] however, studies assessing overall ST using objective measurement methods are lacking.

Furthermore, Antwi et al. (2019) compared the fitness level in young CCS to controls and reported lower fitness in young CCS (Hedges's g = -1.435) when including eight studies in a meta-analysis. However, outcome variables ranged from CRF and MSF to motor performance and physical functioning. Only two of the studies assessed CRF using standardized procedures ($VO_{2\text{-peak}}$ test), of which they found a 4 and 8% lower CRF in young

CCS compared to controls, respectively. A systematic review by van Brussel et al. (2005) included studies assessing CRF using standardized procedures (n = 3), albeit in CCS of ALL only, and found that young CCS had a 13% lower $VO_{2\text{-peak}}$ compared to controls.[67] Concerning MSF, Sönthgerath et al. (2015) systematically reviewed studies in children, adolescents, and young adult CCS. Among studies that included children and adolescents only, six of eight studies reported lower muscle strength in at least one strength test in CCS compared to controls.[68]

In summary, there is a limited body of evidence on levels of PA/ST, CRF, and MSF among adolescent CCS. In particular, studies on PA/ST are limited by subjective measurement methods, which are associated with biases such as social desirability, recognition, and memory.[76] Furthermore, data from self-reports is not suitable for assessing details of PA, such as dose and intensity. Lastly, PA is often assessed as meeting (or not meeting) certain recommendations, such as the WHO's guidelines on PA.[77] As "every minute counts" in terms of health outcomes,[77] dichotomizations of PA will result in a lack of sufficient information.

Long-term effects influencing physical activity, fitness, and sedentary time

There are numerous ways that cancer treatment may impact PA and fitness in both the short and long term. The most relevant example is bone sarcomas treated by surgical amputation or limb-sparing procedures.[61] Moreover, spinal surgery increases the risk of spinal deformity.

Due to the fact that children and adolescents are still developing bones and muscles/soft tissue, these tissues are highly sensitive to radiation, especially the epiphyseal growth plates.[30] Thus, irradiation of bones and soft tissue may affect growth, and deformities and underdevelopment may occur together with an asymmetrical appearance. Furthermore, thoracic irradiation may lead to impairments in pulmonary function,[78] and thus, CRF.

Anthracyclines, which are effective chemotherapeutic drugs commonly used in the treatment of childhood cancer, may induce cardiotoxicity (i.e., inability of the heart to pump blood through the body effectively) and thus impair CRF. Moreover, high-dose steroid treatment may lead to bone fracture due to bone demineralization (osteoporosis).[22]

Thus, bodily impairment and physical limitations may reduce opportunities to participate in PA.[79] In addition, absence from social life and PA/sports in childhood due to cancer treatment may lead to reduced motivation for PA due to perceived ability gaps between survivors and their peers.[79] Furthermore, numerous studies have reported severe fatigue as a common late effect in young CCS, summarized in a Cochrane review from 2020.[80] Qualitative interviews

from the current study population within our study group aiming to explore self-management skills reported that survivors managed their fatigue by securing rest through adapting their activities and activity level, thereby limiting their participation in everyday life.[79] Van Dijk-Lokkart et al. longitudinally assessed the development of cancer-related fatigue, PA, and ST (using activity monitors) in children and adolescents recruited during or within the first year after treatment.[81] They found that increased PA levels from baseline to 12 months follow-up were associated with less fatigue, suggesting that balancing fatigue with less PA may be counter-effective.

1.6 Associations between physical activity and fitness with CVD risk factors

In children and adolescents with no history of cancer, PA and CRF are shown to be independently associated with both single and clustered CVD risk factors.[82-86] This suggests that PA and CRF affect CVD risk through different pathways. For instance, PA may improve an individual's level of blood glucose by improving glucose uptake in working muscles, whereas CRF may improve glucose levels by increasing the muscles' ability to metabolize glucose.[65]

Due to former cancer treatment and the fact that long-term effects may affect both the musculoskeletal and the cardiorespiratory system, we cannot extrapolate the evidence from the general population to CCS, and one may speculate whether the associations between PA and fitness with CVD risk factors are different in CCS compared to the general population.

A few studies of young adult CCS have reported an inverse association between PA and adiposity, whereas findings have been inconsistent for other CVD risk factors.[52,87-89] Slater et al. observed the same result in adolescent CCS (n = 319, mean age 9-18 years).[90] However, most of these studies were limited by self-reporting and dichotomization of PA.[52,87,88,90]

Studies assessing associations between different domains of fitness, such as CRF and MSF, and CVD risk factors in adolescent CCS are lacking. In studies of young adult CCS, low CRF was associated with adiposity, whereas the results were divergent for other CVD risk factors.[52,53,87] Notably, one of the studies estimated CRF using a six-minute walking test and dichotomized CRF as high vs. low.[87] To our knowledge, only one study has assessed the association between MSF and CVD risk factors, albeit in young adult CCS.[53] Schindera et al. found that low MSF was associated with adiposity, triglycerides, and metabolic syndrome.

1.7 Need for new knowledge

Physical activity is suggested as a strategy to diminish late effects from cancer treatment. However, evidence for low PA/high ST in adolescent CCS based on robust measurement methods is low. Thus, there is a need for detailed knowledge concerning device-measured PA in this population. Studies with large sample sizes and a heterogeneous group of CCS are scarce. Large sample sizes, including various childhood cancer diagnoses, are important to obtaining precise estimates and ensuring analyses that enable stratification by important factors, such as age, sex, and diagnostic group, to identify potentially vulnerable subgroups.

Whether an unfavorable CVD risk profile is present already in adolescent CCS is not well studied. Moreover, little is known about the associations between PA and fitness with CVD risk factors in this population and whether the associations are different in survivors compared to healthy peers. This thesis serves to fill important gaps in knowledge by presenting a high-quality analysis of PA, fitness, and CVD risk factors in adolescent CCS.

1.8 Aims of this thesis

The overall aim of this thesis was to increase knowledge concerning PA, fitness, and CVD risk in adolescent CCS. The specific aims of the three papers were as follows:

Paper I

1. To describe levels of device-measured PA and ST in the to-date largest European sample of adolescent CCS, stratified by socio-demographic and cancer-related factors.
2. To examine factors associated with lower MVPA and higher ST in CCS.
3. To compare levels of PA and ST with age- and sex-stratified references.

Paper II

1. To compare CVD risk factors in adolescent CCS with age- and sex-stratified references.
2. To examine the associations between device-measured PA intensities and CVD risk factors in CCS.

Paper III

1. To compare CVD risk factors in adolescent CCS to age- and sex-matched controls.
2. To examine whether the associations of MVPA, CRF, and MSF with CVD risk factors differ between CCS and controls.

2.0 Methods

The three papers that form the basis of this thesis are based on the international, multi-center study *Physical Activity in Childhood Cancer Survivors (PACCS)*, which consists of four work packages (WPs, Figure 3).[91] Paper I is based on WP1, whereas Papers II and III are based on WP2. The paper by Lie et al. gives a detailed description of the entire PACCS project. Methods used in WP1 and WP2 will be described in the following method sections.

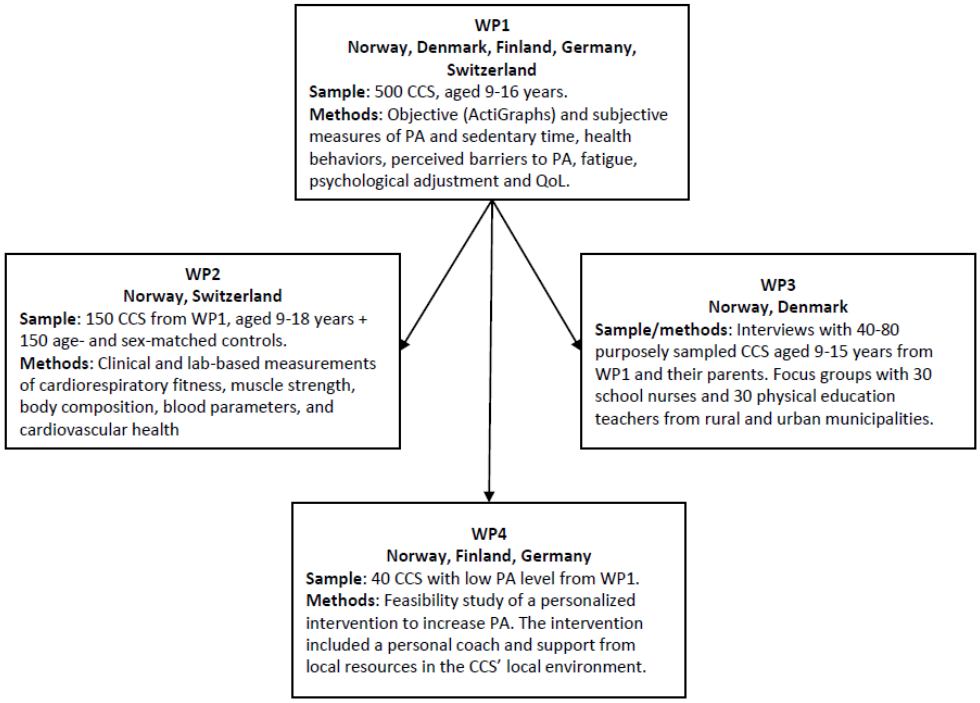

Figure 3: Overview of the participating countries, sample size, and methods for the four work packages (WPs) of the PACCS project.

Abbreviations: CCS, childhood cancer survivors; PA, physical activity; QoL, quality of life; WP, work package.

2.1 Study design and recruitment

All papers used a cross-sectional design, but with a retrospective collection of cancer-related information from the time of diagnosis and treatment.

In WP1, CCS were recruited through scheduled follow-up visits at Oslo University Hospital, Norway; Haukeland University Hospital, Norway; Copenhagen University Hospital, Denmark; Turku University Hospital, Finland; Tampere University Hospital, Finland; University Hospital Essen, Germany; and University Children's Hospital Basel, Switzerland.

In WP2, CCS were recruited accordingly and from the same study sites in Norway and Switzerland. Moreover, age- and sex-matched controls were also recruited. In Oslo and Bergen, controls were recruited via the CCS and were typically a friend or relative of the CCS. In Basel, controls were recruited through the hospital staff from the local community. Participant recruitment and data collection were performed from Oct. 2017 to Dec. 2020 in WP1 and from Jan. 2019 to Jan. 2021 in WP2. In Oslo, CCS were recruited to WP1 and WP2 in the two respective periods. In Bergen, the recruitment process was similar to that in Oslo for approximately half of the participants. Midway through the recruitment process, CCS were recruited to participate in WP1 and WP2 combined. In Basel, all participants were recruited to WP1 and WP2 combined.

Inclusion criteria for CCS in WP1 and WP2 were a history of any cancer diagnosis, ≥ 1 year since cancer treatment completion, and attendance at outpatient follow-up care. In WP1, the age span for inclusion was 9-16 years, whereas in WP2, the age span was 9-18 years. In WP2, an additional inclusion criterion was the ability to perform a cardiopulmonary exercise test (CPET). Exclusion criteria were language difficulties (questionnaires in main native language of each participating country) or limited cognitive function that made it impossible to complete the questionnaire or wear an accelerometer.

2.2 Power calculations

In WP1, power calculations were based on an average PA level of 549 ± 180 counts per minute (cpm) in nationally representative samples of Norwegian nine- and 15-year-olds.[92] To detect a difference of 10% in total PA between CCS and controls (494 vs. 549 cpm, SD = 180 for both groups) with 80% power and a significance level of 5% (one-sided), we had to include 250 CCS. We aimed to include ≥ 500 CCS to enable sub-group comparisons.

In WP2, power calculations were based on an expected 10% lower $VO_{2\text{-peak}}$ in CCS compared to controls, based on results from international studies.[93] To detect a difference of 10% in $VO_{2\text{-peak}}$ between CCS and controls (41.1 vs. 45.7 $mL \cdot kg^{-1} \cdot min^{-1}$, SD = 5.6 for both groups) with 80% power and a significance level of 5% (two-sided), we had to include 23 participants in both groups. We aimed to include 150 CCS and 150 controls to enable sub-group comparisons.

2.3 Measurements

In WP1, participants answered an electronic questionnaire during their follow-up visit at their local hospital and were equipped with an accelerometer to wear the following week. In WP2, the test battery was more extensive than in WP1 (Table 1). CCS participants in Oslo and Bergen participated in the tests over two days, whereas in Basel, all tests were performed on the same day. Controls from Oslo and Bergen participated on the second test day only.

Table 1: Overview of the assessments performed in Oslo, Bergen, and Basel in WP1 and WP2. The colors indicate which tests were performed on the same day[a].

WP1	WP2	Assessment	Oslo	Bergen	Basel
	x	Medical examination (Relevant background information from medical records, i.e., diagnosis and treatment, was also extracted)	x	x	-
	x	Cardiac examination	x	x	x
	x	Pulmonary function tests	x	x	-
	x	Blood sampling	x	x	x
	x	Neuropathy grading	x	x	-
	x	Pulmonary function tests (controls)	x	x	-
	x	Exercise flow volume loops	-	-	x
	x	Dual-energy X-ray absorptiometry	x	x	x
	x	Skinfold assessment	-	-	x
	x	Ultrasound muscle thickness	x	x	-
	x	Functional muscle strength	x	x	x
	x	Isometric muscle strength	x	x	x
	x	Cardiopulmonary exercise test	x	x	x
	x	Blood volume	x	x	-
	x	Blood sampling, extra	x	x	-
x	x	Accelerometry	x	x	x
x	x	Questionnaire	x	x	x

Abbreviation: WP, work package.

a: In Oslo and Bergen, blue and orange color indicates tests performed on the first and second test day, respectively.

Standard operating procedures were developed for each assessment to ensure standardized and high-quality data collection across study sites. Test batteries for WP1 and WP2 are described in detail by Lie et al.[91] Measurements relevant to this thesis are described below, with the following structure: general information on the measurements, which variables we extracted and how, information concerning validity and/or reliability, and lastly, how the variables were defined in the different papers.

Physical activity and sedentary time

At all study sites, ActiGraph GT3X+ (ActiGraph LLC, Pensacola, FL) accelerometers were used to assess participants' levels of PA and ST. The GT3X+ model has sensors that detect acceleration measured in gravity forces (G values) in the vertical, horizontal, and perpendicular axes. The accelerometers were initialized in ActiLife software version 6 (ActiGraph LLC, Pensacola, FL) to collect seven days of data in one axis (vertical) and to sample raw signals at 30 Hertz (30 registrations per second). No filters were applied.

Participants received oral and written instructions to wear the accelerometer around their waist and to situate the monitor on the right side (Image 1). Participants were further instructed to wear the monitor for seven full days to maintain their normal PA level and to remove the monitor during sleep and water-based activities only. The accelerometers were initialized to start data collection the following day to reduce reactivity, a bias that refers to increased PA due to the feeling of being monitored.[94] The participants received a prepaid, addressed envelope to return the accelerometer by postal mail.

Images 1: The ActiGraph accelerometer used to register physical activity in PACCS (left), together with written instructions for wear (right).

Raw data was downloaded and averaged over the defined epoch length (10 and 60-second in the current papers, see below) using ActiLife, where G values are converted into activity counts (Image 2). The number of counts for a given time unit, for example, cpm, reflects the intensity of the activity. Intensity cut-off values for sedentary, light, moderate, and vigorous activities are based on metabolic energy equivalents (METs).[95] One MET is equivalent to an adult's average oxygen consumption during rest (3.5 $mL \cdot kg^{-1} \cdot min^{-1}$), whereas light, moderate, and vigorous-intensity activities are defined as < 3, 3-5.99, and ≥ 6 METs, respectively.

Determining equivalent cut-off values for cpm is based on calibration studies assessing both oxygen consumption through indirect calorimetry and cpm using accelerometers.[96,97]

Raw data and epoch data from each study site was uploaded to one common secure server at the Norwegian School of Sports Sciences for further processing.

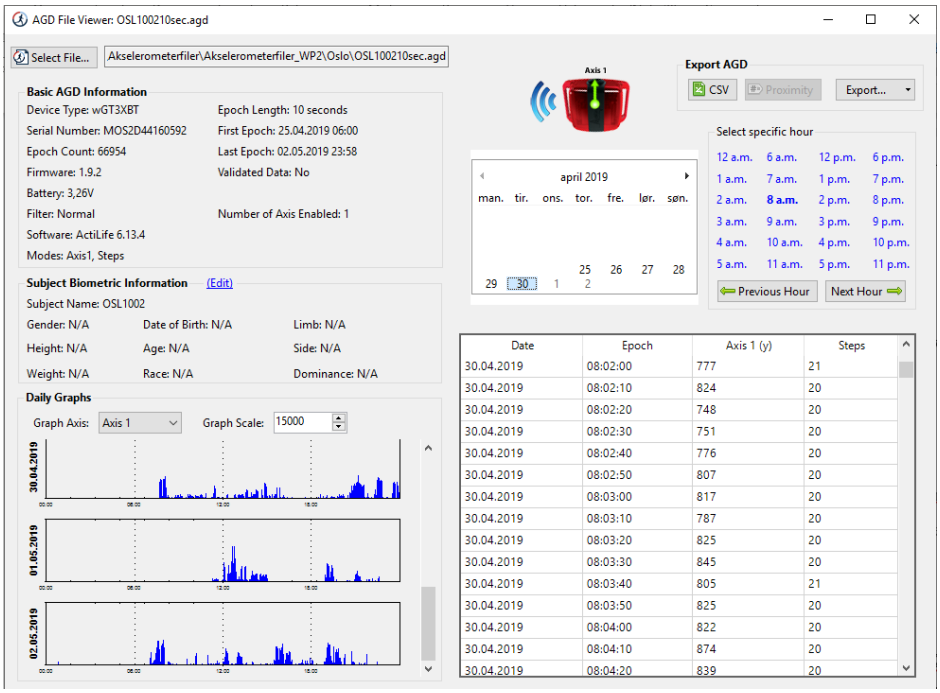

Image 2: Output showing accelerometer epoch data in ActiLife

Epoch data was further processed in KineSoft (version 3.3.80; KineSoft, Loughborough, UK) to define non-wear time, a valid day of wear, and cut-points for ST, light-intensity PA (LPA), moderate-intensity PA (MPA), vigorous-intensity PA (VPA), and MVPA, and to produce hour-by-hour summary data (Table 2).

In Paper I, we used two sets of processing criteria: to describe PA and ST in the CCS only, we used criteria most commonly applied in children and adolescents (Table 2);[98] to compare PA and ST in the CCS to European references, we used the same set of criteria as was applied in the reference material.[99] In Papers II and III, we used criteria applied in previous surveillance studies of PA and ST in Norwegian children and adolescents, thereby enabling future comparison.[92]

Table 2: Overview of processing criteria used in the different papers

	Paper I	**Papers II and III**
Wear protocol	6:00-00:00 hour protocol (excluding night-time)	6:00-00:00 hour protocol (excluding night-time)
Registrational axis	Vertical	Vertical
Epoch length	10-sec / 60-sec	10-sec
Non-wear time	20 min of consecutive zeros, not allowing any interruptions / 60 min of consecutive zeros allowing 2 min of non-zero interruptions	20 min of consecutive zeros, not allowing any interruptions
Valid day	≥ 480 min	≥ 480 min
Number of valid days to be included in the analyses	1 day	3 days
Cut-off points (cpm)	Evenson[96]	Trost[97]/Andersen[83]
ST	< 101	< 100
LPA	101-2295	100-1999
MPA	2296-4012	2000-5999
VPA	≥ 4012	≥ 6000
MVPA	≥ 2296	≥ 2000

Abbreviations: cpm, counts per minute; LPA, light-intensity physical activity; MPA, moderate-intensity physical activity; MVPA, moderate-to-vigorous physical activity; ST, sedentary time; VPA, vigorous-intensity physical activity.

Processed files from KineSoft were gathered and exported to an Excel spreadsheet that was further imported to Stata (version 16.0; StataCorp LP, College Station, Texas) to remove potential activity at night, to transform hour-by-hour data into average daily minutes spent in the different activity levels, and to generate the variable mean cpm as total counts in valid days/total wear time (minutes) in valid days. Based on average daily minutes spent in MVPA, we also generated a variable for meeting the WHO's recommendations for PA, defined as engaging in ≥ 60 minutes of MVPA on average per day.[77] Moreover, we generated a variable for season based on the first day of accelerometer data collection, categorized as 1) Winter (Dec.-Feb.), 2) Spring (March-May), 3) Summer (June-Aug.), and 4) Autumn (Sept.-Nov.).

To decide the number of valid days required for the analyses, participants' mean total PA (cpm) with 95% confidence intervals (CI) according to their number of valid days was calculated using Stata's *margins* command, and the *marginsplot* was used to eyeball

the data visually. In WP1, participants with only one valid day had similar mean cpm as those with two to seven days (Figure 4A), whereas in WP2, participants with < 3 valid days had different mean cpm compared to participants with three to seven valid days (Figure 4B). Thus, for Paper I (WP1), one valid day was required for participants to be included in the analyses, whereas for Papers II and III (WP2), three valid days were required.

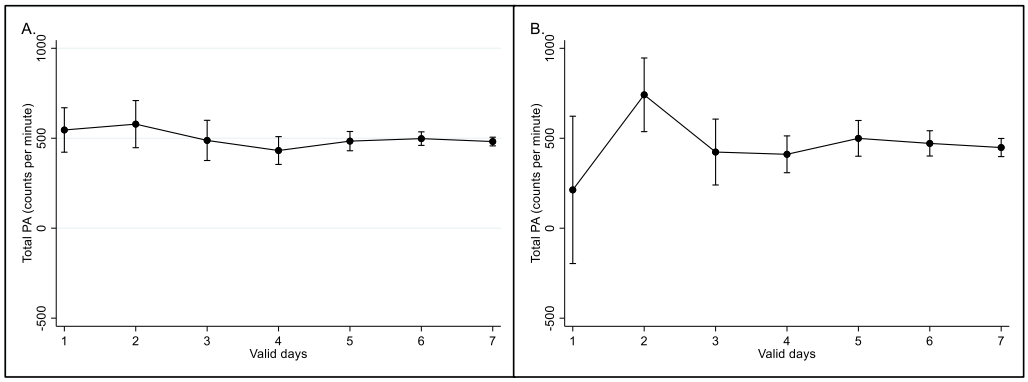

Figure 4: Participants' total physical activity (mean counts per minute with 95% confidence intervals) according to their respective number of valid days in A: work package 1 (n = 432) and B: work package 2 (n = 251).

Validity of uniaxial ActiGraph accelerometers is good for common physical activities and walking in young adults (R^2 = 0.65 and 0.82, respectively) when assessing activity counts by accelerometry to METs by indirect calorimetry.[95,100] Moreover, the combination of 20 minutes of consecutive recorded zeros for non-wear time (recommended for children, as they usually don't sit still for longer time intervals[101]) and a minimum of eight hours of wear to define a valid day, together with a short (15-second) epoch length, has been shown to give a reliable estimate of children's habitual PA (reliability coefficient of 0.90).[102]

Measures of PA are included in all papers in this thesis. In paper I, MVPA and ST were defined as outcome variables, where we examined factors associated with lower MVPA and higher ST. Wear time and season were defined as covariates.

In papers II and III, LPA/MPA/VPA and MVPA, respectively, were defined as exposure variables, where we examined the association between PA and CVD risk factors.

Cardiorespiratory fitness

Cardiorespiratory fitness was assessed by CPET, which includes testing of both pulmonary function and oxygen consumption during exercise. The CPET was performed to volitional fatigue using continuous incremental protocols on a treadmill (modified Balke protocol for children[103] in Oslo and Bergen) or a cycle ergometer (Godfrey protocol[104] in Basel).

From CPET, we extracted the participant's $VO_{2\text{-peak}}$ value ($L \cdot min^{-1}$). $VO_{2\text{-peak}}$ is defined as the highest rate of oxygen consumption attainable during physical exertion and is considered the single best indicator of CRF. Gas exchange was determined by breath-by-breath sampling (Jaeger Oxycon Pro, Viasys Healthcare GmbH, in Oslo, or Jaeger Vyntus CPX, Vyaire Medical GmbH, in Bergen, or Cortex MetaLizer 3B, in Basel) averaged over 30-second intervals through a breathing mask (Hans Rudolph Inc, 2700 series, Image 1).

Image 3: Participant during cardiopulmonary exercise testing

Measurements of BP were performed every two minutes during the test. Participants were asked to rate their level of exhaustion according to Borg's $scale_{6\text{-}20}$ every two minutes during the test and after termination. The reason for exhaustion (lungs, legs, or both) was also noted. Criteria for aborting the CPET were decreasing systolic BP (SBP) or multiple ventricular extrasystoles during the test.

An incremental treadmill-based $VO_{2\text{-}max}$ test is considered the gold standard for assessing CRF.[105] In children and adolescents, the test is often termed $VO_{2\text{-}peak}$ as children do not necessarily achieve a plateau in VO_2 values,[106] which is a common criterion in adults to define a valid test. Other common criteria to define a valid, maximal $VO_{2\text{-}peak}$ test are a respiratory exchange ratio of ≥ 1.0 and/or achieving ≥ 85% of maximum predicted heart rate.[107,108] However, we did not use any of those criteria to judge a maximal test, as this could lead to exclusion of survivors with potential clinical limitations to achieving $VO_{2\text{-}peak}$ according to the set criteria.[109] In non-cancer adolescents (11-16-year-olds), $VO_{2\text{-}peak}$ values obtained from cycling are shown to be 11-14% lower than those obtained from treadmill;[110] however, this has not been tested in adolescent cancer survivors.

The CPET equipment was volume- and gas-calibrated daily to ensure valid measurements, and the tests were performed by qualified test personnel according to standardized procedures. There was always an extra person helping during CPET, both for safety reasons and for intense cheering to ensure maximal effort.

In Paper II, CRF expressed as maximal oxygen uptake capacity ($VO_{2\text{-}peak}$) was defined as an outcome variable (CVD risk factor), where we examined the association between PA and CRF. Absolute values of $VO_{2\text{-}peak}$ were standardized to body mass ($mL \cdot kg^{-1} \cdot min^{-1}$) to facilitate comparison to the reference material of interest.[111]

In Paper III, CRF was defined as an exposure variable, together with MVPA and MSF, to assess MVPA/CRF/MSF's relationship to CVD risk factors in CCS and controls. In this paper, values of $VO_{2\text{-}peak}$ were standardized to fat-free mass ($mL \cdot kg\ FFM^{-1} \cdot min^{-1}$) to avoid confounding from adiposity when comparing CCS to controls.[110]

Musculoskeletal fitness

Musculoskeletal fitness was measured by maximal isometric knee extension and chest press (Images 4-5) on an ergometer bench specifically designed for children (GYM2000, Vikersund, Norway).

Participants were instructed to continuously perform the tests with maximal effort for five seconds. At least three attempts, with a 60-second break, were performed in each isometric exercise until maximal force was achieved. The highest value (kg) in each exercise was registered. The criteria for a valid attempt was flattening of the force curve at the highest force achieved without systematic fluctuations.

Participants' maximal values obtained from knee extension and chest press were summarized and standardized to body weight to generate the variable "total kg pushed" as a proxy of total body MSF.

Images 4: Positioning to execute maximal isometric knee extension. Published with consent from photographer Idunn Lyng Brekken.

Images 5: Positioning to execute maximal isometric chest press. Published with consent from photographer Idunn Lyng Brekken.

There is no gold standard for assessing MSF in children. However, unpublished data from our institution reported a coefficient of variance of 6% for knee extension and 7% for chest press in athletic 12- and 13-year-olds (n = 16), suggesting that these maximal isometric strength exercises are reliable. In Paper III, MSF (kg) was defined as an exposure variable to examine its relationship with CVD risk factors.

Adiposity

Adiposity was assessed as body mass index (BMI, kg/m^2) and android fat mass (FM, g).

Prior to the dual-energy X-ray absorptiometry (DXA) measurement, we measured participants' height (cm) and weight (kg) using a stadiometer and a digital scale, respectively, to calculate BMI.

Android FM was measured by DXA. In Oslo and Bergen, scans were performed by Lunar iDXA (GE Healthcare, Madison, WI) using enCORE software versions 14 and 18. In Basel, scans were performed with Horizon A (Hologic Inc., Bedford, MA) using the InnerCORE software version 13. Participants were measured non-fasted and while wearing light clothing. Potential metal artifacts were removed. Scans were performed from head to toe in a supine position.

The DXA machines automatically separated the body scan into different regions of interest. Android FM is detected within the android region of interest (Image 6),[112] defined as 20% of the distance from the pelvis line (lower boundary) to the head line (upper boundary). In Oslo and Bergen, regions of interest were confirmed or corrected if necessary, whereas in Basel, this was not done. It is unknown whether manual correction of regions of interest impacts measurement error in the android region of interest.

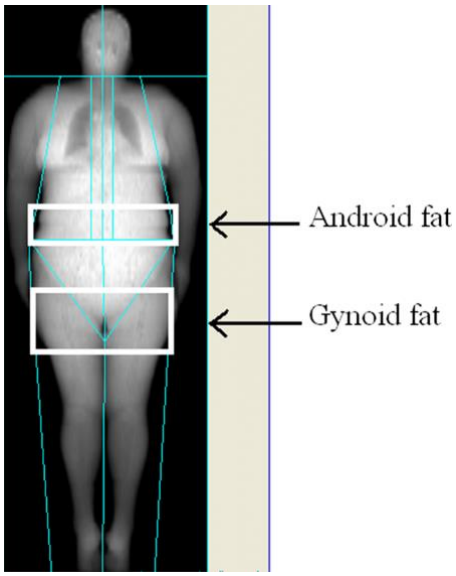

Image 6: Regions of interest supplied by the enCORE software

Lunar iDXA has demonstrated that the level of visceral adipose tissue correlates closely with that obtained by magnetic resonance imaging (gold standard) in an adolescent population (r = 0.82 with underestimation of visceral adipose tissue)[113] and in populations with or without metabolic syndrome (r = 0.98).[114] Less is known about the validity of Horizon A.

In Paper I, adiposity was defined as an exposure variable, where we examined the relationship between BMI category and MVPA/ST. Height and weight were measured non-fasted and in light clothing with a stadiometer and a digital scale, respectively. Values of BMI were converted into iso-BMI categories (age- and sex-adjusted values of childrens' BMI equivalent to adult BMI categories) according to the International Obesity Task Force cut-offs.[115]

In Paper II, adiposity was defined as an outcome variable, where we examined the relationship between PA intensities and BMI (continuous). BMI was used as a measure of adiposity to enable comparison to the reference material of interest.[111]

In Paper III, adiposity was also defined as an outcome variable, where we examined the relationship between MVPA/CRF/MSF and android FM. Android FM was used as a measure of adiposity because it is shown to be more closely correlated with visceral adipose tissue than more traditional measures, such as BMI and waist circumference.[116]

Blood pressure

Participants in Oslo and Bergen did BP (mmHg) measurements on two occasions, first, during a medical visit, and second, prior to CPET. In Basel, participants only took BP measurements prior to CPET. All BP devices used were oscillometric devices, which are shown to have good inter-rater reliability and are the preferred method when assessing BP in research and clinical settings.[117]

Blood pressure may vary considerably according to environmental, behavioral, and psychological factors, such as room temperature, PA, body position, and stress.[118] Hence, standardized BP measurements were performed after a five-minute rest in a temperate room in a seated position (no crossed legs) with back support and the arm resting in the lap.

In Paper II, BP measurements (mmHg) from medical visits in Oslo (Welch Allyn ProBP 3400 series, and Siemens SC 7000) and Bergen (CSI Criticare eQuality model 506 DN (automated) and Welch Allyn (manually)) and prior to CPET in Basel were assessed.

In Paper III, where we compared CCS to controls, BP measurements prior to CPET were assessed for all study sites as controls did not have medical visits; thus, they had only one BP registration (Oslo and Basel: Tango+, Suntech Medical Instruments; Bergen: Tango M2, Suntech Medical Instruments).

Blood sampling

In Oslo, CCS did two blood samplings, one on each test day, with a mean of 5.3 days apart. We used blood values from test day 2 if they were available. If the participant refused to take another blood sample on test day 2 or we did not manage to locate a good vein for sampling, blood values from test day 1 were used for analyses. In Oslo, blood samples from test day 1 were taken in a fasted or non-fasted state, whereas blood samples taken on test day 2 were non-fasted. In Bergen and Basel, blood samples were non-fasted. Blood sampling for controls was mainly performed in Oslo (n = 49) and in a few participants from Bergen (n = 4) in a non-fasted state.

We extracted values of total-cholesterol (mmol/L) and high-density lipoprotein-cholesterol (mmol/L) and combined them to generate a ratio of total-cholesterol to high-density lipoprotein-cholesterol (Total/HDL) as a measure of cholesterol homeostasis. We also extracted values of glycosylated hemoglobin (HbA1c, mmol/mol) as a measure of glucose homeostasis.

In Oslo and Bergen, blood samples were collected by venous sampling, whereas in Basel, samples were collected by venous or capillary samplings. Cholesterol measures were analyzed by photometric methods, and HbA1c was analyzed by high-performance liquid chromatography at medical laboratories.

Venous sampling is often considered the gold standard for collecting blood values. However, the agreement between capillary (whole blood) and venous (plasma) blood samples is found to be very high.[119] For example, in a comparison between the level of total cholesterol in capillary vs. venous samples, the level of total cholesterol was 2.9% higher in the capillary compared to the venous sample.[120] Blood variables to assess lipids and glucose, such as triglycerides and glucose, are affected by the time and content of last meals. However, blood variables assessed in the respective papers (Total/HDL and HbA1c) are mainly unaffected by fasted state.[121,122]

In Paper II, we defined Total/HDL as an outcome variable (CVD risk factor) to assess its association with PA intensities.

In Paper III, we defined Total/HDL and HbA1c as outcome variables to assess their association with MVPA/CRF/MSF.

Puberty stage and parental education

Participants filled out an electronic questionnaire on a computer tablet. We used the Pubertal Development Stages questionnaire to assess indices of pubic hair, voice, and facial hair in boys, and pubic hair, breast development, and menstruation in girls.[123] Participants were categorized as pre-pubertal if the participant reported the lowest category for all indices, post-pubertal if the participant reported the highest category for all indices, and the remaining participants were categorized as pubertal. The Pubertal Development Stages questionnaire shows good validity against the Tanner scale, which is considered the gold standard to assess puberty stage when the scales are combined into three categories.[124]

In Papers II and III, puberty stage was defined as a confounding factor when assessing the association between PA, fitness, and CVD risk.

Parents reported their educational level through an electronic questionnaire, and parental education was used as a proxy for the child's socioeconomic status. Six categories for education level were collapsed into three categories: 1) 9-10 years, 2) 11-13 years, and 3) > 13 years.

In Paper I, parental education was defined as an exposure variable when assessing its association with MVPA and ST.

In Paper II, parental education was defined as a confounding factor when assessing its association between PA intensities and CVD risk.

Information extracted from medical records

Key variables were extracted from participants' medical records in conjunction with recruitment: sex, year and month of birth, cancer diagnostic group (leukemia, lymphoma, CNS tumor, tumor outside CNS), year and month of diagnosis and completed treatment, type of treatment (chemotherapy, surgery, radiation, stem cell transplantation), and recurrence. In WP2, we also extracted information on cumulative anthracycline dose (doxorubicin isotoxic equivalent dose, mg/m^2),[125] radiation dose (Gy), and high-dose steroids (yes/no) as part of the cancer treatment protocol). Based on those variables, we calculated age at study, age at diagnosis (years), time since diagnosis (years), and treatment completion (years).

In Paper I, diagnostic group, age at diagnosis, and recurrence were used as exposure variables to assess survivors' associations with MVPA and ST.

In Paper II, age at diagnosis, cumulative doses of anthracycline and radiation, and high-dose steroid treatment were defined as confounding factors when assessing the association between PA intensities and CVD risk factors.

Other information

Information on participants' resident country, study site, and CCS-control pair (WP2 only) was registered.

In Paper I, country was defined as a covariate when assessing the associations between sociodemographic and cancer-related factors with PA and sedentary time in CCS.

In Paper II, study site was defined as a cluster variable when assessing the association between PA intensities and CVD risk factors in CCS.

In Paper III, study site and CCS-control pair were defined as cluster variables when assessing the association between MVPA/CRF/MSF and CVD risk factors in CCS vs. controls.

2.4 Reference materials

A European reference material harmonized by Steene-Johannessen et al. on total PA, MVPA, and ST was available for comparison of marginal means (Paper I).[99] The study consisted of 47,497 children and adolescents aged 2-18 years from North, Central, and South Europe collected in the period from 1997-2014. We did not have the raw material available, and thus stratified our sample of CCS in accordance to the reference material as sex- and age-stratified (two-year intervals) reference values of the 8/9- to 16/17-year-olds.

A reference material on 14 CVD risk factors, harmonized by Stavnsbo et al. was available for comparison of marginal means (Paper II).[111] The material included 22,479 valid observations of at least one CVD risk factor in children and adolescents aged 6-18 years, mainly from North America and North Europe but also Western Europe (Switzerland) and South Europe (Portugal). The data was collected from 1997-2009. We used sex- and age-stratified (1-year interval) reference values of the 9 to 18-year-olds (n = 5161-9229 in females and n = 5214-9214 in males, depending on the CVD risk factor).

2.5 Statistical analyses

All statistical analyses were performed using Stata statistical software release 16.0 or 17.0 (StataCorp LP, College Station, TX). A two-tailed alpha level of 0.05 was set as the statistical significance level. In all papers, sample characteristics are expressed as means ± standard deviation (SD) or frequency with proportion (%).

In both WP1 and WP2, the comparison of participants vs. non-participants was based on a limited number of available demographic and cancer-related key factors recorded in conjunction with the recruitment of participants (age, sex, age at diagnosis, diagnosis, potential relapse). Comparisons between groups were made by t-tests for unequal variances (Welch's t-tests).

Models made in Papers II and III were based on a directed acyclic graph drawn in Dagitty version 3.0 (www.dagitty.net) (Figure 5) to identify the minimal set of confounders that needed to be included in the models to estimate the total effect. Statistical analyses for the individual papers are described below.

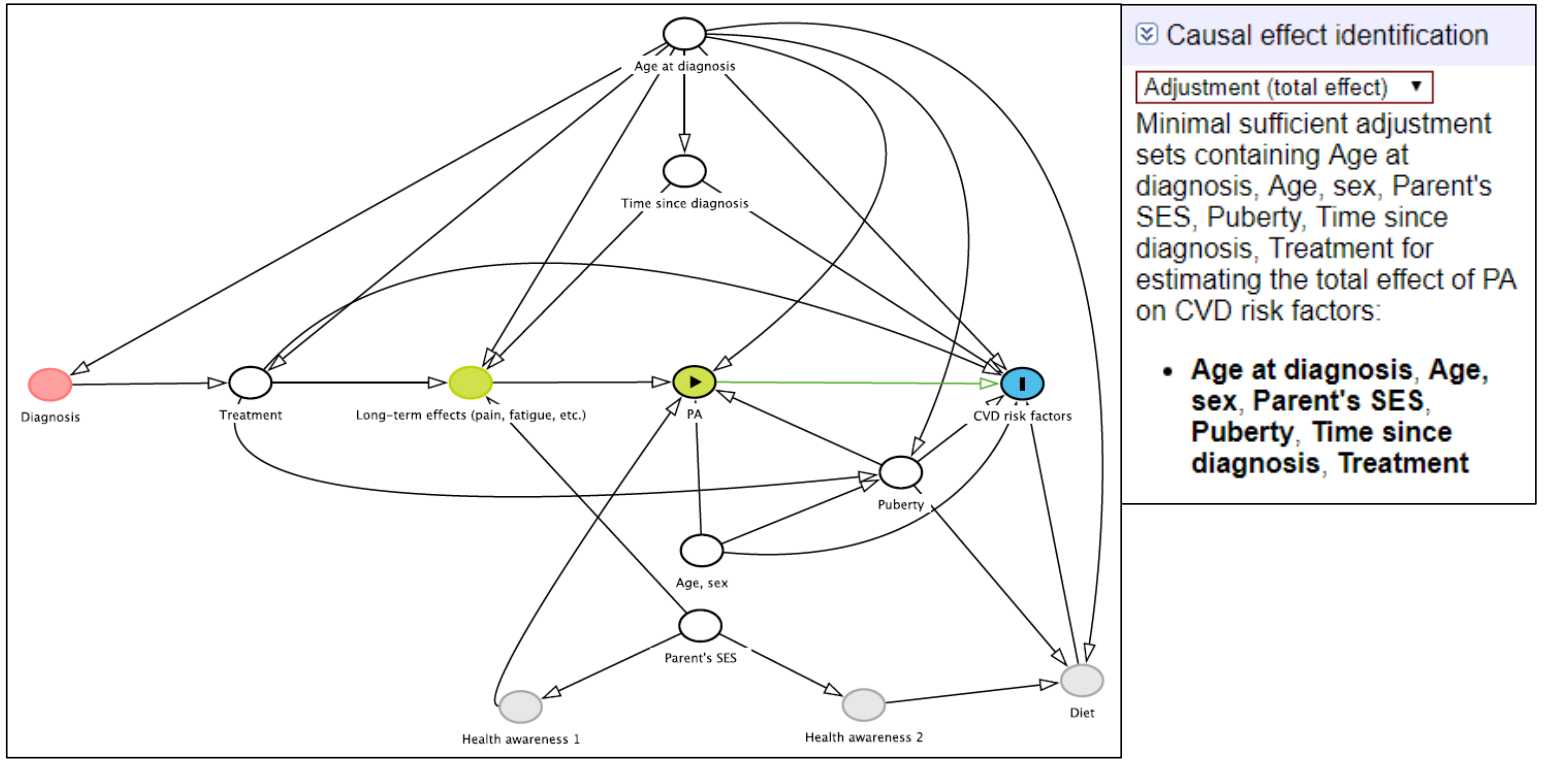

Figure 5: Directed acyclic graph used for model specification in Papers II and III

Abbreviations: CVD, cardiovascular disease; PA, physical activity; SES, socio-economic status.

Paper I

Physical activity and sedentary time in European childhood cancer survivors

Total PA, MVPA, and ST were presented by socio-demographic variables (country, sex, age, iso-BMI, parental education) and cancer-related factors (diagnosis, age at diagnosis, relapse).

We performed univariable and multivariable linear regression models to examine socio-demographic and cancer-related factors associated with lower MVPA and higher ST. Univariable models were adjusted for country, season, and wear time. Multivariable models were additionally adjusted for sex, age, iso-BMI, parental education, diagnosis, age at diagnosis, and relapse. We defined missing information on parental education as its own category to avoid losing participants in the analyses. Global p-values for categorical variables were calculated using likelihood-ratio tests (LRTs). In the multivariable model, we tested each variable for interaction with sex and age category (dichotomized, 9-11 vs. 12-16 years).

Comparison of physical activity and sedentary time to reference material

We compared marginal means of total PA, MVPA, and ST between CCS and references according to sex and age group using immediate Welch's t-tests; a t-test that tests the difference of a variable of interest between two groups based on information of sample size, mean, and SD, if no individual-level data is available. Our analyses were adjusted for country and season. Analyses on MVPA and ST were additionally adjusted for wear time.

Paper II

Comparison of CVD risk factors in CCS to reference population

We described male and female CCS separately to facilitate comparison to the reference material of interest. Comparisons were performed using immediate Welch's t-tests.

Associations between PA intensities and CVD risk factors

We investigated the association between LPA, MPA, and VPA with the following single CVD risk factors. In addition, single CVD risk factors were transformed into z-scores (based on the above-mentioned age- and sex-stratified reference material) to create a CVD risk score as $(Z_{CRF\text{-}inverse} + Z_{BMI} + Z_{SBP} + Z_{Total/HDL}) / 4$. Associations were assessed using mixed effects linear regression models with study site as random intercept to account for clusters in the data. We made three models for each LPA, MPA, and VPA exposure on each of the outcomes CRF, BMI, SBP, Total/HDL, and CVD risk score:

- In Model 1, we adjusted for study site as random intercept only.
- In Model 2, we additionally adjusted for age, sex, puberty stage, and parental education as fixed effects.
- In Model 3, we additionally adjusted for cancer-related variables (age at diagnosis, cumulative anthracycline and radiation dose, high-dose steroids) as fixed effects.

We performed LRTs to compare Models 2 and 3 to investigate the influence of cancer-related characteristics on the PA-CVD risk factor associations.

Paper III

Comparison of CVD risk factors between CCS and controls

To compare CVD risk factors between CCS and controls, we calculated marginal means with 95% CIs and p-values from mixed effects linear regression models, adjusted for study site and CCS/control-pair as random intercepts, and age, sex, and puberty stage as fixed effects.

Association of MVPA, CRF, and MSF with CVD risk factors in CCS and controls

Associations were examined by mixed effects linear regression models, including an interaction term between the exposure (MVPA/CRF/MSF) and participant status (CCS or control). We made two models for each MVPA, CRF, and MSF exposure on each of the outcomes android FM, SBP, Total/HDL, and HbA1c:

- In Model 1, we adjusted for site and CCS-control pair as random intercepts only.
- In Model 2, we additionally adjusted for age, sex, and puberty stage as fixed effects.

2.6 Ethics

The PACCS study was approved by the Norwegian Regional Committee for Medical Research Ethics (WP1: 2016/953 and WP2: 2018/739), and the Data Protection Officer at Oslo University Hospital and by the equivalent institutions in Finland, Denmark (file. H-19032270), Germany, and Switzerland (Ethics Committee of North-Western and Central Switzerland, project-ID 2019-00410). As most of the participants were too young to provide valid informed consent, they received written and verbal information about the studies adapted to their developmental stage, and their guardians provided written consent. Children, and especially CCS, are a vulnerable group. We created a secure environment by meeting the children with respect and attention, and by giving oral information upon their arrival and encouraging and acknowledging their effort during and after the tests.

3.0 Summary of results

The following result sections summarizes the main findings in Papers I-III. For details, the reader is referred to the original papers (included at the end of the thesis).

3.1 Study samples

Of the 726 CCS invited to WP1 (**Paper I**), 432 (60%) contributed with valid data on accelerometry (Figure 6). Reasons for not participating were not asked for; however, among the reasons given were language problems, distance to the study site, COVID-19, not wanting to participate in any further research, wanting to forget about their cancer, or ”having enough on their plate.”

A comparison of basic characteristics (sex, age at study, age at diagnosis, time since diagnosis, diagnostic group) between participants and non-participants in WP1 showed no differences, except that participants were slightly younger at study compared to the non-participants (12.2 vs. 12.6 years, $p = 0.023$).

Of the 267 CCS invited to WP2 (**Papers II** and **III**), 157 (59%) contributed valid data on CVD risk factors, together with the 113 controls (Figure 6). A comparison of basic characteristics between participants and non-participants in WP2 showed no differences.

Comparison of study samples

Both the WP1 and WP2 sample was comprised of about 50% of survivors of leukemia, and almost all participants in both samples had received chemotherapy (Table 3). In WP2, Norwegian participants comprised more of the total sample than in WPI (85 vs. 50%), and participants were older (13.4 vs. 12.2 years). Further, more WP2 participants were categorized as normal weight (75 vs. 64%) and fewer as overweight (11 vs. 23%), and more parents reported having the highest category of education (60 vs. 48%). The samples were similar concerning age at diagnosis, and there was a similar distribution of the diagnostic groups, treatment received, and the proportion who had experienced a relapse.

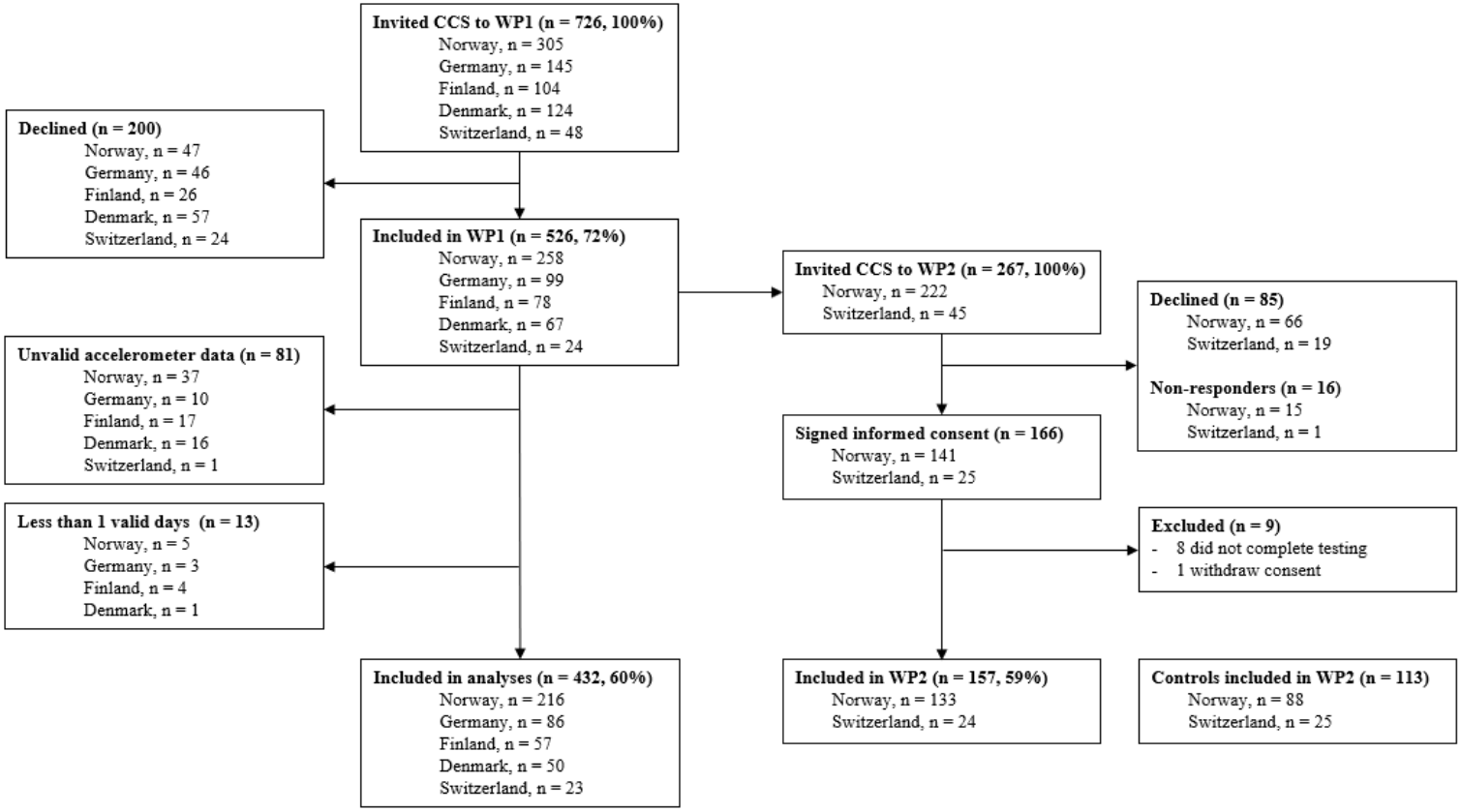

Figure 6: Flowchart of the inclusion process in PACCS WP1 and WP2

Abbreviation: WP, work package.

Table 3: Characteristics of participants in PACCS WP1 and WP2

	N (%) or Mean ± SD	
Socio-demographic characteristics	**WP1 (n = 432)**	**WP2 (n = 157)**
Country		
Norway	216 (50%)	133 (85%)
Germany	86 (20%)	
Finland	57 (13%)	
Denmark	50 (12%)	
Switzerland	23 (5%)	24 (15%)
Sex		
Male	226 (52%)	84 (54%)
Female	206 (48%)	73 (46%)
Age at study (years)	12.2 ± 2.2	13.4 ±2.5
Iso-BMI category		
Underweight	35 (8%)	15 (10%)
Normal weight	276 (64%)	114 (73%)
Overweight	99 (23%)	18 (11%)
Obese	22 (5%)	10 (6%)
Parental education		
9-10 years	41 (12%)	6 (6%)
11-13 years	138 (40%)	32 (34%)
> 13 years	169 (48%)	57 (60%)
Cancer-related characteristics		
ICCC-3 diagnostic group		
I. Leukemia	203 (47%)	78 (50%)
II. Lymphomas	47 (11%)	16 (10%)
III. CNS tumor	69 (16%)	18 (11%)
IV-XII Tumor outside CNS	113 (26%)	45 (29%)
Age at diagnosis (years)	5.1 ± 3.3	5.2 ± 3.4
Treatment		
Chemotherapy	393 (91%)	153 (97%)
Surgery	159 (37%)	60 (38%)
Radiotherapy	97 (23%)	45 (29%)
HSCT	50 (12%)	16 (10%)
Autologous	*18 (4%)*	*10 (6%)*
Allogeneic	*32 (7%)*	*6 (4%)*
Relapse		
No	390 (90%)	144 (92%)
Yes	42 (10%)	13 (8%)

Abbreviations: BMI, body mass index; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; WP, work package.

3.2 Physical activity and sedentary time

Participants in both WP1 and WP2 demonstrated good compliance with the accelerometer wear protocol, with average wear times of about 13 hours/day for six days.

The overall marginal mean of total PA for the CCS was 486 ± 183 cpm/day, and minutes/day spent in MVPA and ST were 54 ± 23 and 523 ± 58, respectively (**Paper I**). In total, 34% of the CCS met the PA recommendation. Compared to the other diagnostic groups, survivors of

CNS tumors spent less time in total PA and MVPA and more time sedentary (Figure 7), while 17% met the PA recommendation.

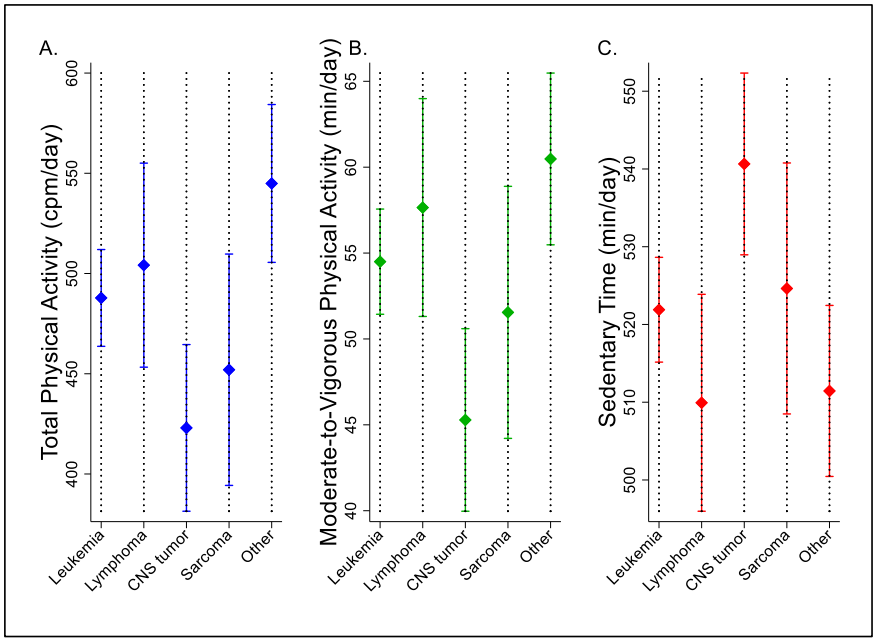

Figure 7: Marginal means (diamonds) with 95% confidence intervals (whiskers) for A. total physical activity, B. moderate-to-vigorous physical activity, and C. sedentary time in childhood cancer survivors, stratified by diagnostic group (n = 432).

Abbreviations: cpm, counts per minute; CNS, central nervous system; Other, other cancer diagnosis (includes neuroblastoma (n=18), renal tumor (n=30), liver tumor (n=4), retinoblastoma (n=14), germ cell tumor (n=2), carcinoma (n=3), and "other" (n=6)).

Notes: The models are adjusted for age, sex, country, and season. Analyses on MVPA and ST are additionally adjusted for wear time.

In CCS, being female, overweight, a survivor of CNS tumor, and having experienced a relapse were associated with lower MVPA. Similarly, being female, older (12-16 vs. 9-11 years), overweight, and being a survivor of CNS tumor were associated with higher ST.

In general, male CCS had lower levels of total PA and MVPA than the references, whereas female CCS were similar to the references (Figure 8). Both male and female CCS spent more time sedentary compared to the references.

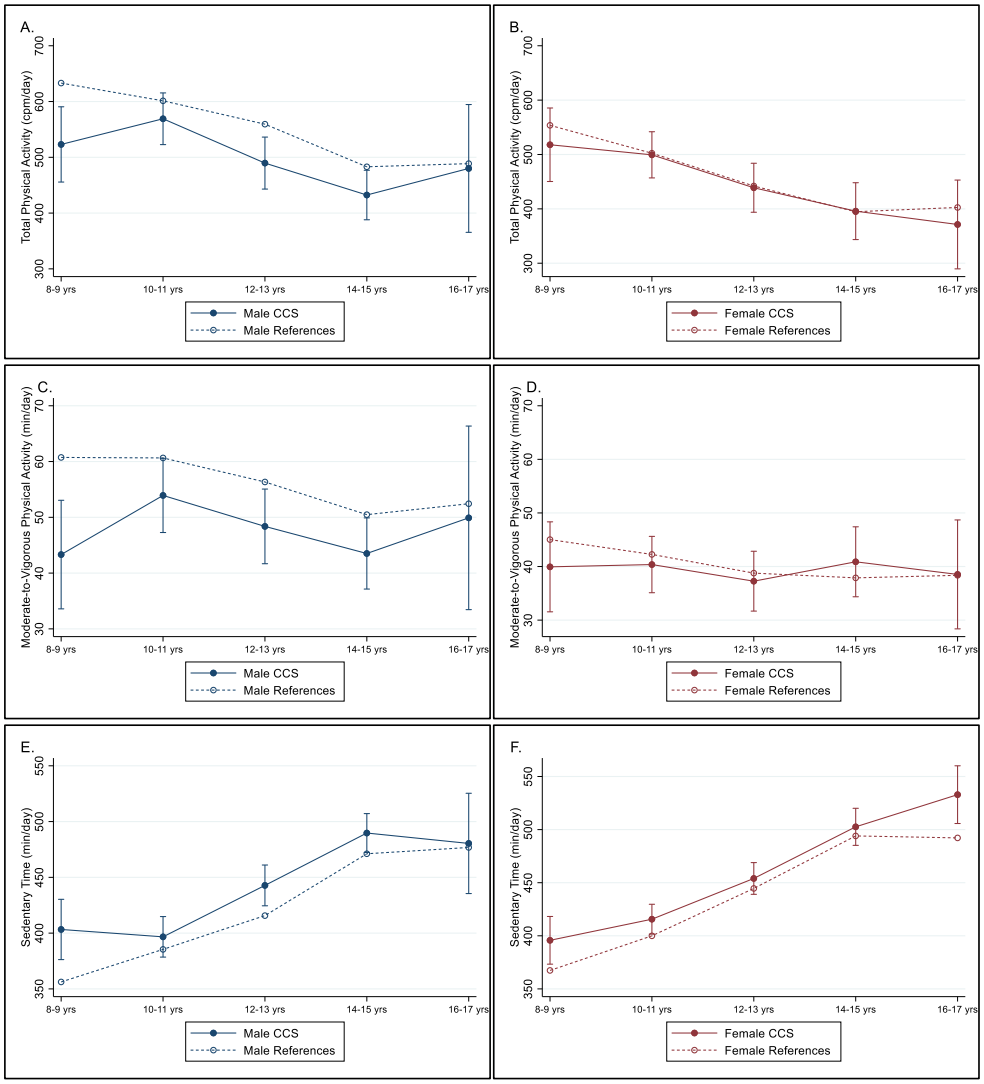

Figure 8: A-B. total physical activity (cpm), C-D. moderate-to-vigorous physical activity, and E-F. sedentary time in childhood cancer survivors (solid lines, n = 432) and references[99] (dashed line), stratified by sex and age category*. Note: Graphs represent cross-sectional data.

Abbreviations: CCS, childhood cancer survivors; cpm, counts per minute; n, number.

Notes: Dots represent marginal means, and whiskers represent 95% CIs. Analyses are adjusted for country and season. Analyses on moderate-to-vigorous physical activity and sedentary time are additionally adjusted for wear time. Female CCS, n = 206; Male CCS, n = 226.

*In the age category 8-9 years, only two 8-year-old CCS are included. In the age category 16-17 years, only four 17-year-old CCS are included.

3.3 Cardiovascular disease risk factors

Compared to the references (**Paper II**), male CCS had lower $VO_{2\text{-peak}}$ (z-score = -0.52 vs. 0.00, P = 0.001), as well as a tendency to higher CVD risk score (z-score = 0.14 vs. 0.00, P = 0.075), whereas BMI, SBP, and Total/HDL were similar (Figure 9). Female survivors' CVD risk factors were similar to the references.

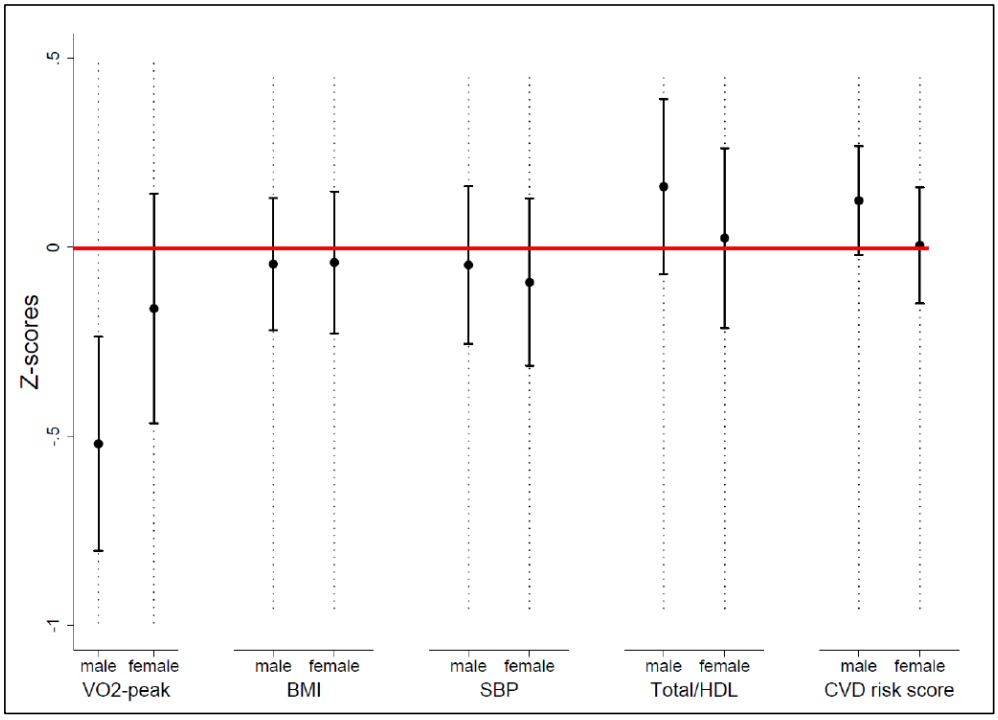

Figure 9: Mean z-scores with 95% confidence intervals for single CVD risk factors and the CVD risk score in childhood cancer survivors compared to references (red line), stratified by sex.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; SBP, systolic blood pressure; Total/HDL, ratio of total-cholesterol to high-density lipoprotein-cholesterol.

Note: Z-scores of VO2-peak in the CVD risk score are based on inverse values.

Compared to the controls (**Paper III**), CCS had higher levels of android FM and lower SBP (Table 4). Total/HDL and HbA1c were similar between CCS and the controls.

Table 4: Marginal means of CVD risk factors with 95% confidence intervals in childhood cancer survivors and controls

	CCS (n = 154)	**Controls (n = 112)**	
CVD risk factors	**Mean (95% CI)**	**Mean (95% CI)**	**P-value**
Android fat mass (g)	861 (770-952)	648 (542-754)	0.001
Systolic BP (mmHg)[a]	114 (106-121)	118 (111-126)	0.002
Total/HDL[b]	3.1 (2.9-3.2)	2.9 (2.7-3.1)	0.23
HbA1c (mmol/mol)[c]	33 (32-35)	34 (32-36)	0.19

Abbreviations: BP, blood pressure; CCS, childhood cancer survivors; CI, confidence interval; CVD, cardiovascular disease; HbA1c, glycosylated hemoglobin; Total/HDL, total-cholesterol/high-density lipoprotein-cholesterol.

Marginal means with 95% CIs and p-values from mixed effects linear models with study site and CCS/control-pair as random intercepts and age, sex, and puberty stage as fixed effects.

a: Missing value for Systolic BP in four CCS and three controls. b: Missing value for Total/HDL in four CCS and 54 controls.

c: Missing values for HbA1c in four CCS and 55 controls.

Note: Blood samples were drawn from controls mainly from Oslo, hence the large number of missing Total/HDL and HbA1c values in this group.

3.4 Association between physical activity and CVD risk factors

All PA intensities were associated with higher $VO_{2\text{-peak}}$ in CCS (**Paper II**), and the coefficients increased in size with higher intensity PA (Table 5). Both MPA and VPA were associated with lower Total/HDL, and MPA was additionally associated with lower SBP. Adding cancer-related characteristics to the model (Model 3) resulted in a better model fit (P_{LRT} comparing models = 0.002). However, adding cancer-related variables to the model did not affect the associations between PA intensities and CVD risk factors, except that it reduced the strength of the associations between higher intensities of PA (MPA and VPA) and $VO_{2\text{-peak}}$ (P_{LRT} comparing models = 0.011 and 0.004, respectively).

Table 5: Association between 10-minute increase in physical activity intensities/day and CVD risk factors in childhood cancer survivors

	10 min LPA (n = 137)			10 min MPA (n = 137)			10 min VPA (n = 137)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
	β -coefficients with 95% CIs								
$VO_{2\text{-peak}}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)[a]	0.4 (0.0 to 0.7)	0.5 (0.1 to 0.8)	0.5 (0.1 to 0.8)	1.2 (0.6 to 1.8)	1.3 (0.7 to 1.9)	1.0 (0.4 to 1.6)	5.5 (2.5 to 8.6)	5.6 (2.6 to 8.5)	4.9 (2.1 to 7.7)
BMI (kg/m^2)	−0.2 (−0.3 to −0.1)	−0.1 (−0.2 to 0.1)	−0.0 (−0.2 to 0.1)	−0.3 (−0.5 to −0.0)	−0.1 (−0.3 to 0.1)	−0.1 (−0.3 to 0.2)	−1.1 (−2.3 to 0.2)	−0.8 (−2.0 to 0.3)	−0.8 (−2.0 to 0.3)
SBP (mmHg)[a]	−0.5 (−0.8 to −0.1)	−0.1 (−0.5 to 0.3)	−0.1 (−0.5 to 0.2)	−1.0 (−1.6 to −0.3)	−0.8 (−1.4 to −0.2)	−0.9 (−1.5 to −0.3)	−2.2 (−5.7 to 1.2)	−1.8 (−5.0 to 1.3)	−2.0 (−5.1 to 1.2)
Total/HDL[b]	−0.0 (−0.1 to 0.0)	−0.0 (−0.0 to 0.0)	−0.0 (−0.0 to 0.0)	−0.1 (−0.1 to −0.0)	−0.1 (−0.1 to −0.0)	−0.1 (−0.1 to −0.0)	−0.4 (−0.7 to −0.1)	−0.3 (−0.6 to −0.1)	−0.3 (−0.6 to −0.1)
CVD risk score[c]	−0.0 (−0.0 to 0.0)	−0.0 (−0.1 to 0.0)	−0.0 (−0.1 to 0.0)	−0.1 (−0.1 to −0.0)	−0.1 (−0.1 to −0.0)	−0.1 (−0.1 to −0.0)	−0.4 (−0.6 to −0.1)	−0.4 (−0.6 to −0.2)	−0.4 (−0.6 to −0.2)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; LPA, light-intensity physical activity; MPA, moderate-intensity physical activity; SBP, systolic blood pressure; Total/HDL, ratio of total-cholesterol to high-density lipoprotein-cholesterol; VO2-peak, peak oxygen consumption; VPA, vigorous-intensity physical activity.

Model 1 is adjusted for study site.

Model 2 is additionally adjusted for age, sex, puberty stage, and parental education.

Model 3 is additionally adjusted for age at diagnosis, cumulative anthracycline dose, radiation dose, and high-dose steroid treatment (yes/no).

a: Missing information on VO2-peak (unknown reason) and SBP in two participants.

b: Missing information on Total/HDL in six participants.

c: CVD risk score was set to missing for one participant due to < 3 CVD risk factors.

In CCS (**Paper III**), a 10-minute higher MVPA/day was associated with a lower level of android FM (-52 g, 95% CI, -85 to -19, Figure 10) and Total/HDL (-0.1 mmol/L, 95% CI, -0.1 to -0.0), and higher SBP (0.7 mmHg, 95% CI, 0.0 to 1.4). There was no association between MVPA and HbA1c.

The associations between MVPA and CVD risk factors were similar between CCS and the controls (all $P_{interactions} > 0.05$), although none of the associations were significant in the controls.

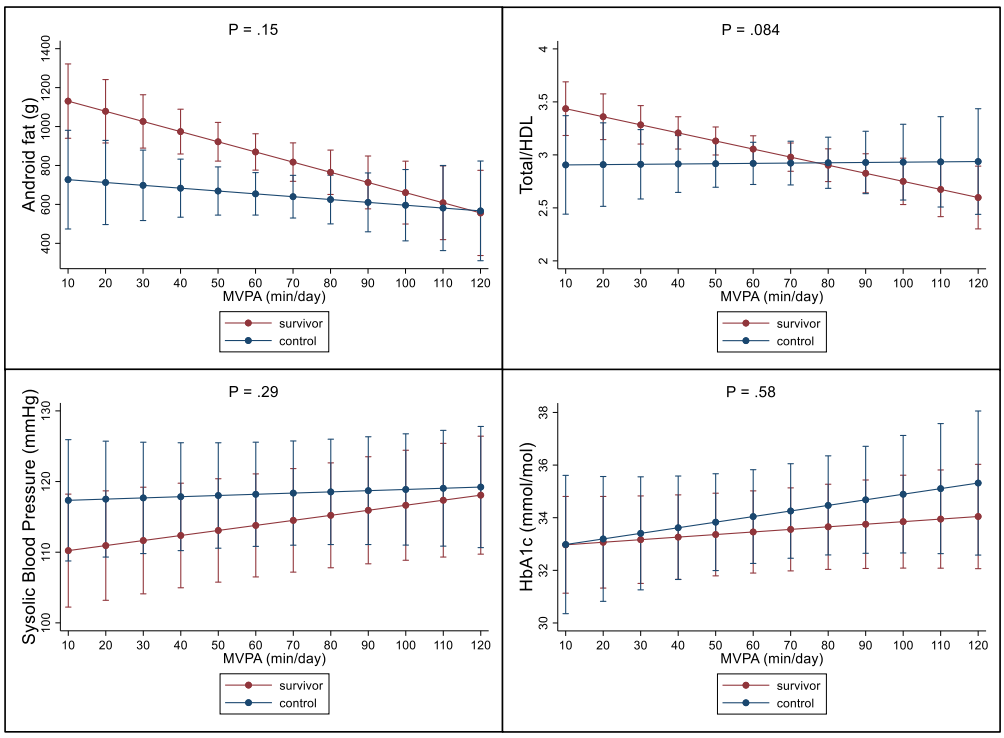

Figure 10: Associations of moderate-to-vigorous physical activity with android fat mass (upper left), Total/HDL (upper right), systolic blood pressure (lower left), and HbA1c (lower right) in childhood cancer survivors vs. controls.

Abbreviations: MVPA, moderate-to-vigorous physical activity; P, p-value for interaction; Total/HDL, ratio of total-cholesterol to high-density lipoprotein-cholesterol.

Notes: Dots represent marginal means with 95% CIs from mixed effects linear regression models with study site and survivor-control pair as random intercepts, age, sex, and puberty stage as fixed effects, and interaction term between exposure (MVPA) and participant status (survivor or control). Depending on the exposure variable, the number of survivors varied from n = 131-135, and the number of controls varied from n = 52-102.

3.5 Association between fitness and CVD risk factors

In CCS (**Paper III)**, a higher $VO_{2\text{-peak}}$ of 5 mL·FFM^{-1}·min^{-1} was associated with a lower level of android FM (-145 g, 95%, -193 to -97, Figure 11) and Total/HDL (-0.1, 95% CI, -0.2 to -0.1), and higher SBP (1.6 mmHg, 95% CI, 0.6 to 2.6). $VO_{2\text{-peak}}$ was not associated with HbA1c.

In the controls, higher $VO_{2\text{-peak}}$ was associated with higher SBP (1.6 mmHg, 95% CI, 0.4, 2.9) but not with the other CVD risk factors. The association between CRF and android FM was stronger in CCS compared to the controls ($P_{interaction}$ = 0.001) but not with the other CVD risk factors.

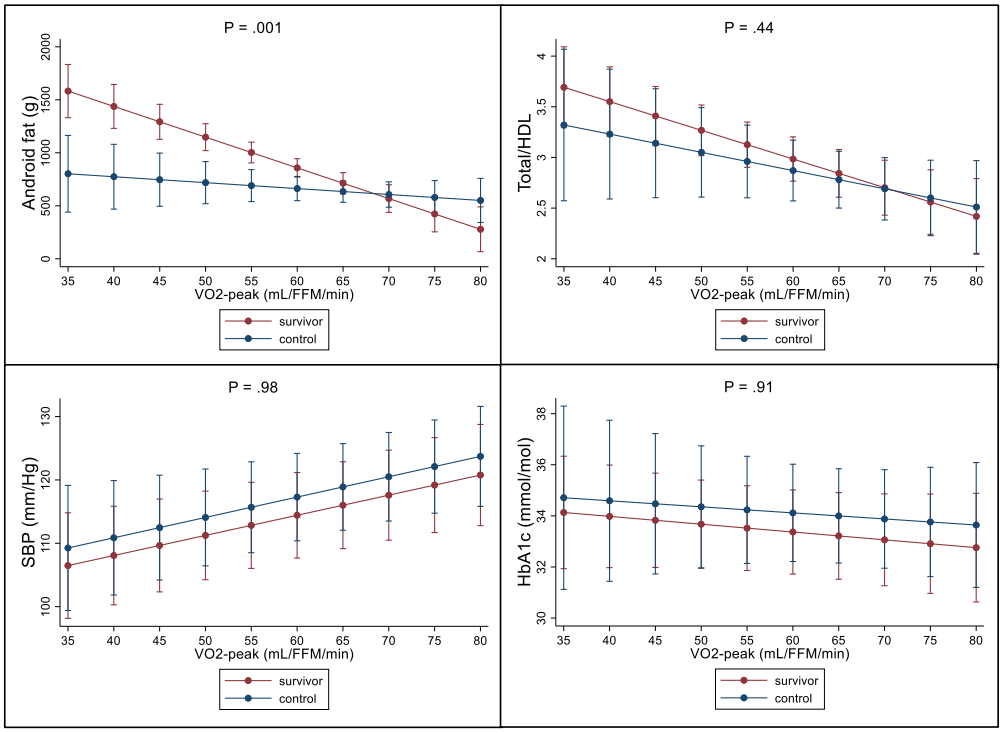

Figure 11: Associations of cardiorespiratory fitness ($VO_{2\text{-peak}}$) with android fat mass (upper left), Total/HDL (upper right), systolic blood pressure (lower left), and HbA1c (lower right) in childhood cancer survivors vs. controls.

Abbreviations: FFM, fat-free mass; P, p-value for interaction; Total/HDL, ratio of total-cholesterol to high-density lipoprotein-cholesterol; VO2-peak, peak oxygen uptake.

Notes: Dots represent marginal means with 95% CIs from mixed effects linear regression models with study site and survivor-control pair as random intercepts, age, sex, and puberty stage as fixed effects, and interaction term between exposure (CRF) and participant status (survivor or control). Depending on the exposure variable, the number of survivors varied from n = 146-152, and the number of controls varied from n = 57-110.

In CCS (**Paper III**), a higher MSF of 0.25 total kg pushed·kg^{-1} was associated with a lower level of android FM (-302 g, 95% CI, -361 to -243, Figure 12) and Total/HDL (-0.2 mmol/L, 95% CI, -0.3 to -0.1), and higher SBP (1.6 mmHg, 95% CI, 0.2 to 2.9). MSF was not associated with HbA1c.

In the controls, higher MSF was associated with a lower level of android FM (-142 g, 95% CI, -272 to -74). However, the association between MSF and android FM was stronger in CCS compared to the controls ($P_{interaction} < 0.001$). Higher MSF was not associated with any of the other CVD risk factors in controls, and the associations were similar in CCS and the controls.

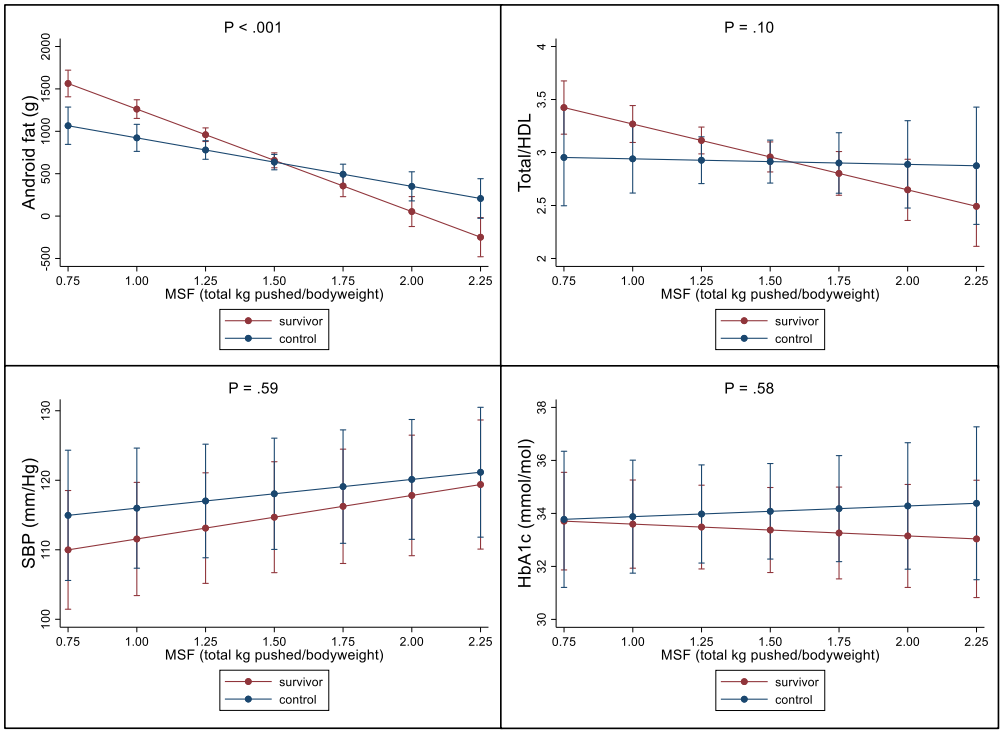

Figure 12: Associations of musculoskeletal fitness with android fat mass (upper left), Total/HDL (upper right), systolic blood pressure (lower left), and HbA1c (lower right) in childhood cancer survivors vs. controls.

Abbreviations: MSF, musculoskeletal fitness; P, p-value for interaction; Total/HDL, ratio of total-cholesterol to high-density lipoprotein-cholesterol.

Notes: Dots represent marginal means with 95% CIs from mixed effects linear regression models with study site and survivor-control pair as random intercepts, age, sex, and puberty stage as fixed effects, and an interaction term between exposure (MSF) and participant status (survivor or control). MSF was calculated as ((maximal isometric knee extension (kg) + maximal isometric chest press (kg) / body weight (kg)). Depending on the exposure variable, the number of survivors varied from n = 143-147, and the number of controls varied from n = 56-109.

4.0 General discussion

The overall aim of this thesis was to increase the knowledge of PA, fitness, and CVD risk in adolescent CCS. In the following, a discussion of the main results in separate sections in light of relevant literature, together with relevant methodological issues will be given. Further, the generalizability of the current studies will be discussed, followed by the strengths and limitations.

4.1 Physical activity and sedentary time

Within this international sample of adolescent CCS, only a third met the WHO's recommendation for PA, and the CCS spent most of their day sedentary (**Paper I**). Factors associated with both less MVPA and/or more ST were being female, older, overweight, having had a diagnosis of CNS tumor, and having experienced a relapse.

The lack of literature concerning device-measured PA and ST in adolescent CCS hinders comparisons of our findings. However, sociodemographic factors (being female, older, or overweight) associated with less MVPA and/or more ST are in line with the literature on the general adolescent population. The only modifiable factor we examined was BMI. If we assume a directional association between MVPA/ST and BMI, helping overweight CCS to become more physically active and less sedentary may improve their health, which is important in this population at high long-term risk of CVD.[126,127]

Survivors of CNS tumors were less physically active compared to the other diagnostic groups, and fewer met the PA recommendation. This stands in contrast to results by Mizrahi et al., where the diagnostic group of adolescent CCS was not associated with meeting or not meeting the PA recommendation.[128] However, PA was assessed by parental reports, which may explain the difference in our findings. Moreover, they found that parents of CCS perceive their children to be more physically active compared to parents of healthy control children, which could be due to a stronger social desirability bias in parents of children previously affected by cancer. The findings of Mizrahi et al. emphasize the importance of using devices to (more objectively) measure PA in this population. Moreover, cancer relapse was associated with lower MVPA. This is in line with Schindera et al., who found that self-reported PA was lower in CCS who had experienced a relapse.[129] In summary, our results suggest that sociodemographic variables seem equally important as the cancer-related variables for MVPA and ST.

Physical activity and sedentary time in childhood cancer survivors compared to references

Comparing CCS to the references (**Paper I**), male survivors were less physically active (both total PA and MVPA), whereas female survivors had equally low levels of PA. Importantly, male and female survivors in all age groups registered more ST than the references.

Previous studies using self-reported data have shown that adolescent and young adult CCS are less physically active than their siblings or peers.[130,131] Our results support these findings, albeit in male CCS only. A recent publication examining barriers and facilitators of PA within a subset of the current population (n = 63, mean age 14 years) reported that perceived reduced bodily function, together with fatigue, were barriers to PA, leading to fewer opportunities to participate in PA. Moreover, CCS perceived an ability gap between themselves and their peers that reduced their motivation to participate in PA, such as team sports and physical education at school.[79]

A methodological issue to be considered is the use of accelerometer data averaged over 60-second epochs. A short epoch (e.g., 10-second) is recommended in children and adolescents to capture short bouts of PA that are common in these age groups.[98] Thus, the level of MVPA in CCS and the references may have been underestimated, as shown in our paper, where we applied both versions of processing criteria to the CCS (Supplemental results Paper I). Moreover, the non-wear criterion affects wear time, which further impacts ST because longer wear time generally leads to an accumulation of more ST. For example, a study by Aadland et al. found that the non-wear criterion of 60:2 minutes (and 20:0 minutes) underestimated ST by 5% compared to the non-wear criterion of 60:0.[132] Thus, the level of ST in CCS and the references may also have been underestimated. This shows the importance of using the same settings and procedures when comparing accelerometer results between different populations. In our study, using the same criteria for CCS as used in the reference material, we can assume that the underestimation of MVPA and ST was similar in both CCS and references and will thus not have impacted the comparison between groups. Until a long-awaited consensus on common accelerometer settings in children and adolescents is reached, reporting detailed information about settings used in research studies is crucial.

4.2 Cardiovascular disease risk factors

Compared to the references (**Paper II**), male CCS had lower $VO_{2\text{-peak}}$ and a tendency towards a higher CVD risk score. BMI, SBP, and Total/HDL were similar between male CCS and references. Female CCS and the references had similar levels of the single CVD risk factors and the CVD risk score.

Compared to the controls (**Paper III**), CCS had substantially more android FM and lower SBP, whereas levels of Total/HDL and HbA1c were similar.

Results from previous systematic reviews comparing CRF in adolescent CCS and controls are in line with our findings, namely, that CRF is lower in CCS compared to controls.[66,67] Moreover, our finding of a higher level of adiposity in CCS compared to controls aligns with the previous studies in adolescent CCS.[90,133] Even though we found a higher level of android FM in CCS compared to the controls, level of BMI was similar in CCS compared to the references. Slater et al. reported similar findings: adolescent CCS had a higher level of adiposity compared to their sibling controls in terms of waist circumference and body fat percentage but not in regards to BMI.[90] Furthermore, they found a lower level of lean body mass in CCS compared to their sibling controls. A higher level of adiposity in adolescent and young adult CCS compared to controls was also reported by Talvensaari et al. in terms of body fat percentage.[133] Our results, together with the results by Slater et al., suggest that BMI may not be an appropriate measure of adiposity, and we support the recommendation to use DXA to assess adiposity in this population.[134]

To our knowledge, no studies have compared Total/HDL in adolescent CCS and controls previously. However, two previous studies assessing HDL-c found a similar level in young adult CCS and controls,[51,87] whereas three studies found lower levels in adolescent and young adult CCS compared to controls.[46,50,133] To our knowledge, only one study has compared HbA1c in CCS to controls previously. Chow et al. reported higher HbA1c in a large sample of young adult CCS compared to references.[135] Levels of glucose, and hence, HbA1c, are well-regulated in adolescents, as the pancreas can maintain its ability to secrete elevated amounts of insulin for years or decades before hyperglycemia manifests.[136] Thus, the age difference between our study samples may explain the differences in our findings, and may further indicate that HbA1c is insensitive to detect unfavorable changes in glucose homeostasis in adolescents.

The diverging results showing similar SBP between CCS and the references (**Paper II**) but lower SBP in CCS compared to the controls (**Paper III**) might be explained by the use of

SBP values from the medical visit for the Norwegian participants (Oslo and Bergen) in Paper II, whereas we used SBP values prior to CPET in Paper III. By comparing values of SBP during the medical visit and prior to CPET for the Norwegian participants, we saw that the values were significantly higher prior to CPET than during the medical visit, especially among CCS from Oslo, who contributed the most data to the study. Basel participants, who only measured BP prior to CPET, had comparable values of SBP to those who measured BP at the medical visits in Norway. This implies that the procedure for measuring BP prior to CPET in Basel was different than in Norway; for example, Basel participants had a longer resting period prior to the BP measurement, and that SBP values prior to CPET in Norway did not reflect resting SBP. The BP devices used prior to CPET in Oslo and Bergen are likely suitable for following the progression of BP during a test; however, they might not be appropriate for generally measuring resting BP.

Nonetheless, we were surprised to find lower values of SBP in CCS compared to controls, as they were assessed using the same BP devices and under equal conditions. A recent study by Chow et al. found a similar lower value of SBP among a large sample of young adult CCS (n = 571) compared to references. However, our result contrasts with most previous studies where BP values were similar[87,133] or higher[50,51,137] in adolescent and/or young adult CCS vs. controls or references. During puberty, BP increases more rapidly compared to pre- and post-pubertal phases,[138] and if cancer treatment has affected the progression of puberty (i.e., slower pubertal development),[139] this might partly explain the difference in SBP values between CCS and the controls. It is possible that our adjustment for the rather crude and self-reported puberty stage was not sensitive enough to completely account for puberty progression, and there might have been some residual confounding.

4.3 Associations between physical activity and CVD risk factors

Cardiorespiratory fitness

In the CCS, all PA intensities were associated with CRF (**Paper II**). To our knowledge, no studies on the relationship between PA and CRF in adolescent CCS have been conducted. However, in young adult CCS, an intervention study by Järvelä et al. found that an increase in self-reported PA of about 5 MET-hours/week (corresponding to ~30 minutes of VPA/week or ~4 minutes of VPA/day[140]) was associated with a 5% increase in $VO_{2\text{-peak}}$ ($mL \cdot kg^{-1} \cdot min^{-1}$).[56] This is in line with our results, where we found that a 10-minute higher level of daily

VPA was associated with 4.9 $mL \cdot kg^{-1} \cdot min^{-1}$ higher $VO_{2\text{-peak}}$, which corresponds to about 11% (calculated from the CCS' overall mean $VO_{2\text{-peak}}$ of 42.8 $mL \cdot kg^{-1} \cdot min^{-1}$).

Furthermore, we found that adding cancer-related characteristics (age at diagnosis, cumulative doses of anthracycline and radiation, and high-dose steroid treatment) to the multivariable model reduced the strength of the association between higher intensities of PA and CRF (**Paper II**). This might indicate that CCS have smaller increases in CRF in response to higher intensities of PA than adolescents with no history of cancer. Some potential mechanisms induced by cancer treatment may be through impairment in systolic and diastolic function or heart rate response limiting survivors' performance during exercise. Moreover, pulmonary limitations may cause impairments in ventilation and gas exchange, and arterial stiffness and endothelial dysfunction may limit the vascular system.[93]

Adiposity

In **Paper I**, MVPA was associated with lower BMI (category) in multivariable models, whereas in **Paper II**, the associations of LPA and MPA with lower BMI were significant only in univariable models. In Paper II, we adjusted for puberty stage—information we did not have in Paper I. Moreover, the sample size in Paper I was more than triple the size of the sample in Paper II. Hence, the observed association between MVPA and BMI in Paper I might be due to the confounding by puberty stage, or the absence of significant associations in Paper II might be due to a lack of statistical power. However, in **Paper III**, MVPA was associated with less android FM in multivariable models. Slater et al. found that self-reported high PA (≥ 60 minutes of MVPA/day) was associated with lower levels of adiposity (measured as body fat percentage, subcutaneous, and visceral adipose tissue) compared to low PA (< 60 minutes of MVPA/day) in adolescent CCS. Another study by Slater et al., however in young adult CCS, showed similar findings: self-reported high PA (≥ 2.5 hours/week of MVPA) was associated with lower levels of adiposity (measured as waist circumference and body fat percentage) compared to low PA (< 2.5 hours/week of MVPA). The problematic feature of BMI is well known also from the general population, (i.e., more active people develop more muscle mass, which is heavier than FM, thus masking possible associations between PA and adiposity).[141] BMI does not distinguish between FM and FFM, of which the latter is positively associated with PA.[90] This is supported by two studies in young adult CCS. Järvelä et al. reported that a 16-week exercise program reduced levels of adiposity, measured as waist circumference, waist-to-hip ratio, and body fat percentage, but not with BMI.[56] Similarly, Tonorezos et al. found that higher device-measured PA was

associated with lower body fat percentage but not with BMI. Our results, together with results from the abovementioned studies, suggest that there are inverse associations between PA and adiposity in CCS, and we emphasize the use of more sensitive adiposity measures to detect the health effect of increased PA on body composition in this population.

Blood pressure

In **Paper II**, higher MPA was associated with lower SBP, whereas in **Paper III**, higher MVPA was associated with higher SBP. These discrepancies are also reflected in the current literature. Järvelä et al. found that increased PA led to reduced SBP in young adult CCS,[56] whereas two studies by Slater and colleagues found no associations between high vs. low PA and SBP in adolescent[90] and young adult CCS.[87] These results suggest uncertainty regarding the relationship between PA and BP. As BP is lowered by less sympathetic activity and upregulation of nitric oxide-signaling of peripheral arteries,[142] large variations in BP according to environmental, behavioral, and psychological factors[118] may explain the difference in findings and further emphasizes the need for and strict adherence to a standardized measurement protocol.

Blood parameters

A 10-minute increase in higher intensities of PA was associated with 3-9% lower Total/HDL (**Papers II** and **III**). This cholesterol measure in association with PA has not been examined in this population previously. However, Järvelä et al. reported that increased PA led to an 8% increase in HDL-c in young adult CCS.[56] By contrast, both studies by Slater and colleagues found no association between high vs. low PA and any cholesterol measure in adolescent[90] and young adult CCS[87]. The loss of information through dichotomization of PA in both studies by Slater et al. may explain why they did not find any associations between PA and cholesterol.

Moderate-to-vigorous physical activity was not associated with the level of glucose measured as HbA1c (**Paper III**). The association between PA and HbA1c has not been previously examined in adolescent CCS. However, concerning other measures of glucose metabolism, Järvelä et al. reported that increased PA led to reductions of > 30% in both fasting plasma insulin and insulin resistance (HOMA-IR = [fasting glucose units of mmol/L * insulin units in µU/mL] / 22.5[143]), but did not find any reduction in fasting glucose level.[56] Furthermore, in the two studies by Slater and colleagues, they found higher insulin sensitivity, but not lower insulin resistance, in adolescent[90] and young adult CCS[87] who registered high vs. low levels of PA. Altogether, these results indicate that HbA1c (and fasting glucose) is an insensitive

measure to detect associations with PA and that measures of insulin may be more suitable as early indicators of future disease.[136]

Associations between physical activity and CVD risk factors in survivors vs. controls

We found no statistically significant differences in the associations of MVPA and CVD risk factors in CCS vs. controls; however, some of the associations were significant in CCS but not in the controls (**Paper III**).

We found a stronger association between MVPA and adiposity in CCS compared to controls, albeit the interaction term was not significant. This is in line with the two studies by Slater and colleagues, who reported that MVPA was more strongly related to measures of adiposity in both adolescent[90] and young adult CCS[87] compared to their sibling controls. However, they also reported significant interactions. Moreover, MVPA was associated with higher SBP and lower Total/HDL in CCS but not in controls. These findings contrast with the results of the two studies by Slater and colleagues, who did not find any association between high vs. low MVPA and levels of SBP or blood lipids in adolescent or young adult CCS (or sibling controls). Both studies by Slater et al. assessed PA based on self-reported leisure-time PA and dichotomized PA as meeting/not meeting the U.S. recommendation for children or adults, respectively, which might explain the differences in our findings.

We were surprised that we did not find any associations between MVPA and CVD risk factors in the controls, which contrasts with previous studies.[82,83,85] This might be due to an underpowered and selected control sample, especially for analyses of blood parameters.

4.4 Associations between physical fitness and CVD risk factors

In CCS, both CRF and MSF were associated with lower android FM and Total/HDL and higher SBP (**Paper III**). Neither CRF nor MSF was associated with HbA1c. Few studies have examined the relationships between domains of physical fitness and CVD risk factors in adolescent CCS. However, two studies have assessed the association(s) between CRF and/or MSF in young adult CCS. Slater et al. found that high endurance (measured by the 6-minute walking test) was associated with a lower level of adiposity and higher insulin sensitivity compared to low endurance but not with levels of cholesterol or BP.[87] Schindera et al. found that higher CRF (measured by CPET on a cycle ergometer) and MSF (measured by the handgrip test) in young adult CCS were associated with reduced risk of having a high waist circumference and CVD risk score. Higher CRF was additionally associated with reduced

risk of having low HDL-c. They did not find any associations between higher CRF or MSF and the risk of having high BP or high fasting glucose level. As both CRF and BP increase naturally during puberty,[138,144] this might explain why the associations between CRF and BP in adolescents vs. young adults are different. Moreover, differences in measurement methods of CRF and MSF (and the dichotomization of CVD risk factors) may explain the differences in results. As the 6-minute walking test involves less cardiorespiratory efforts compared to CPET, in addition to a known ceiling effect,[145] and the handgrip test involves less muscle mass compared to isometric strength tests of thigh and chest, they may be less valid measures of CRF and MSF and may therefore mask possible relationships between CRF/MSF and CVD risk factors.

Associations between physical fitness and CVD risk factors in survivors vs. controls

Associations of CRF and MSF with CVD risk factors were similar in CCS and controls, with the exception of a stronger association between CRF/MSF and android FM in CCS. More android FM in CCS may explain why the associations between CRF/MSF and android FM were stronger in CCS than in controls. In line with our findings, Slater et al. also reported that CRF was more strongly related to waist circumference in adult CCS compared to sibling controls.[87]

In controls, CRF was associated with higher SBP but not with android FM, Total/HDL, or HbA1c. Musculoskeletal fitness was associated with lower android FM but not with SBP, Total/HDL, or HbA1c. This stands in contrast to results from studies in the general population, where both CRF and MSF were found to be associated with both single and clustered CVD risk factors.[82,84,146,147] A potential selection bias in controls in terms of having higher fitness levels than the general population could have led to potential non-findings due to "optimal" levels of CVD risk factors (ceiling effects). Moreover, as with MVPA, the lack of associations between domains of fitness and several CVD risk factors might be due to an underpowered control sample, especially in terms of blood parameters, or due to too little variation in the exposure (MVPA/CRF/MSF) or outcome (CVD risk factors).

4.5 Generalizability

We compared basic characteristics (sex, age, age at diagnosis, time since diagnosis, and diagnostic group) between participants and non-participants in both WP1 and WP2. Except for a slightly younger age in participants compared to non-participants in WP1, participants did not differ from non-participants, supporting the generalizability and external validity of our findings. However, the participation rates of about 60% in both WP1 and WP2 might indicate selection bias in our samples, with CCS interested in PA and fitness being more inclined to participate in such a study (especially for WP2 where the ability to perform a CPET was an inclusion criteria). Moreover, generalizability is limited to CCS attending follow-up care, speaking their country of residence's main language, and without cognitive impairments.

The sample in both WP1 and WP2 consisted of CCS mainly from Northern European countries. Parental health literacy (judgments/decisions in everyday life concerning healthcare, disease prevention, and health promotion) is an important factor associated with positive health behavior in children and adolescents, including healthy nutrition and PA.[148] Studies have shown that health literacy is higher in Northern European countries (i.e., Norway, Denmark, Finland) compared to Western European countries (i.e., Germany, Switzerland),[149] indicating that we may have selected samples with above European average health literacy, leading to better health behaviors.

The distribution of diagnostic groups within our sample does not reflect the real distribution of childhood cancer diagnoses in Norway (Figure 1). We sampled comparably more leukemia and fewer CNS tumor survivors. As CNS tumor survivors were less physically active and more sedentary compared to the other diagnostic groups, the overall estimates of levels of PA/ST and CVD risk factors among adolescent CCS might have been biased.

The use of reference materials for levels of PA/ST from 1997-2014 (**Paper I**) and CVD risk factors from 1997-2008 (**Paper II**) might have been inappropriate for comparing our samples, as we do not know whether these reference materials reflect the general adolescent population of today. Temporal trends for PA in Norwegian 9- and 15-year-olds from 2005-2018 suggest that adolescents' PA levels were fairly stable or slightly declining in this period.[150] A continuation of a stable or slightly declining PA level in the general population will have resulted in reasonable estimation or a slight overestimation, respectively, of the difference between levels of PA in CCS compared to the general population (**Paper I**). Temporal trends of CVD risk factors in the European *adult* population from 1980-2014 found

an overall decrease in BP from around 2008-2014, stable total-cholesterol levels between 2000-2009 (no data after 2009), and increases in BMI throughout the entire period (1980-2014).[151] If CVD risk factors in the European *adolescent* population follow the same trends as in the adult population, we might have underestimated the difference in BP and BMI between CCS and the general population (**Paper II**).

Taken together, these potential selection biases might have led to an overestimation of PA and an underestimation of ST and CVD risk in our sample of adolescent CCS.

4.6 Strengths and limitations

Strengths

In WP1 (**Paper I**), the main strength was the relatively large sample of adolescent CCS from different diagnostic groups. Previous research in adolescent CCS has mainly been limited to survivors of ALL, limiting the generalizability of findings to the whole population of CCS. In WP2 (**Papers II** and **III**), our sample was smaller; however, the inclusion of controls was a major strength. Moreover, the inclusion criteria that the CCS had to be at least one year away from cancer treatment completion makes our results more reliable concerning both levels of PA/ST and CVD risk factors.[62,73]

Other strengths were the use of valid and reliable measurement methods to assess several CVD risk factors and levels of PA, CRF, and MSF. Accelerometry-measured PA has clear advantages over self-reporting, eliminating biases such as social desirability, recognition, and memory. CPET is considered the gold standard for assessing CRF, and isometric knee extension and chest press are reliable measures of whole-body MSF. Moreover, we had access to medical records, giving us valid medical data compared to self-reported medical data in other studies. The availability of medical data allowed us to adjust for potential confounding factors in the analyses and investigate the influence of cancer-related characteristics on our outcomes of interest.

We kept both outcome and exposure variables continuous, which reduced loss of information and risk of misclassification due to categorization or dichotomization. Moreover, using continuous variables in analyses yields greater statistical power to detect true differences between groups or associations between variables, reducing the risk of type II errors (failure to reject the null hypothesis of no difference/no association when there is an actual difference/association (false-negative)).

Limitations

All data given in this thesis is cross-sectional, which is ideal for providing a snapshot of levels of PA and CVD risk factors. However, as data on both exposure and outcome variables were collected at the same time, inferring causal relationships is not possible. Hence, we cannot be sure whether the exposure causes the outcome or vice versa. For example, we found an inverse association between BMI and MVPA (**Paper I**), but whether lower MVPA causes higher BMI or whether higher BMI causes lower MVPA is uncertain. However, we tried to overcome this problem in Paper I by choosing potential associated factors that were chronologically present before the assessment of PA and ST, such as age, sex, parental education, and all the cancer-related information. This inherent timeline between exposure and outcome variables allowed us to interpret them as potential predictors of PA and ST, even though we can still not estimate a causal relationship. A causal relationship can only be estimated in randomized controlled trials or by using causal inference methods in longitudinal observational data. To validate our results and to try to estimate a causal relationship between PA, fitness, and CVD risk factors in adolescent CCS, I would therefore suggest a follow-up assessment of all outcomes and exposures in this cohort to gain valuable and unique longitudinal data. At the same time, new eligible survivors could be enrolled to increase the sample size. This would yield more power in multivariable models and/or allow us to stratify by finer diagnostic or treatment groups.

Even though our sample size was theoretically large enough in Paper I to detect a difference in PA between CCS and references, stratifications on sex and age groups (to enable comparison to the reference material of interest) led to small subgroups and, hence, the risk of type II error. The same risk applies to the multivariable analyses. Moreover, we did not perform separate power calculations for detecting differences in CVD risk factors between survivors and references/controls (paper II-III).

Device-measured PA is superior to self-reporting in terms of estimating doses of PA, however, accelerometers lack the ability to detect water-based activities (e.g., swimming), activities with little vertical acceleration (e.g., cycling), and stationary activities with high load (e.g., strength training). Moreover, wearing an activity monitor could increase PA (reactivity).[152] Even though the accelerometer was worn for seven days, the measured week may not have been representative of the actual long-term PA level due to acute infection, holidays, other pressing duties, or the previously described reactivity behavior. Thus,

although participants were overall compliant with the accelerometer protocol, one week of monitoring may not reflect their true levels of PA/ST.

We failed to find a reference material for HbA1c and were therefore unable to compare a measure of glucose homeostasis, which is a central CVD risk factor, in CCS to references (**Paper II)**. Moreover, we did not collect fasted blood sample values as were done with the references. However, the chosen blood parameters, Total-c and HDL-c, are mainly unaffected by fasted state.[121]

Another limitation was few blood samples from the controls (**Paper III)**. Furthermore, equipment or measurement methods were different between study sites. However, we accounted for this in the analyses by adjusting for study site as a random intercept in mixed models in all of our analyses. In the same manner, we adjusted for CCS-control pairs as a random intercept to account for similarities between CCS and controls that were friends/relatives.

Lastly, we were not able to stratify levels of PA and ST according to treatment intensity in WP1 (**Paper I**), as we would have liked to, since we did not have detailed enough treatment information.

5.0 Conclusions

Based on the findings of this thesis, the following conclusions can be drawn:

Overall, adolescent CCS had unfavorable levels of PA and ST, and only a third met the recommended level of PA of ≥ 60 minutes of MVPA/day, on average (**Paper I**). Risk factors of lower MVPA and/or higher ST were being female, older, overweight, a survivor of CNS tumor, and having experienced a relapse.

Compared to the references, male CCS were less physically active, whereas female CCS had equally low levels of PA (**Paper I**). Importantly, both male and female CCS spent more time sedentary compared to references in all age groups.

Adolescent CCS had more android FM than controls (**Paper III**), and male CCS had a lower CRF compared to the references (**Paper II**). Levels of Total/HDL and HbA1c were similar in CCS and controls/references, whereas values of SBP were higher than in the references but lower than in the controls.

Spending more time in higher intensities of PA was beneficially associated with several CVD risk factors (**Paper II**). Cancer-related characteristics moderated the association between higher intensities of PA and CRF.

The associations between MVPA, CRF, and MSF with CVD risk factors were similar in CCS and controls, except the associations between CRF and MSF with adiposity were stronger in CCS compared to controls (**Paper III**).

Adolescent CCS may benefit more from increasing their CRF and MSF compared to controls, possibly due to a greater potential for reducing android FM (**Paper III**). In addition to MVPA and CRF, we also found that MSF was associated with CVD risk factors, which has not been shown in this population previously.

6.0 Implications

As CCS are already at greater risk of premature morbidity and mortality than the general population; adding the negative health impacts of low PA and high ST may further exacerbate this risk. Hence, CCS should be at least as physically active as the general population. Survivors' disease risk may further be potentiated by low CRF and higher android FM.

Healthcare personnel should have the demonstrated low levels of PA and high ST in mind when addressing follow-up care for CCS, especially in females, older adolescents, those that are overweight, survivors of CNS tumors, and those who have experienced a relapse. Moreover, they should be aware that an unfavorable CVD risk profile may be present already in adolescence.

As adolescence is a crucial period with respect to establishing lifestyle habits, we call for tailored interventions to increase PA and reduce ST in adolescent CCS. This is important, as the deficit in fitness among CCS seems to accelerate further into adulthood.[109]

Knowledge concerning feasible and cost-effective strategies for reducing CVD-related late effects after childhood cancer is needed. Increasing PA and fitness are plausible strategies for this purpose. The current cross-sectional study implies associations between physical activity and fitness with CVD risk factors, however, the direction of the associations may not be inferred. Hence, randomized controlled trials or prospective cohort studies are needed to explore whether increased PA can reduce CVD risk in adolescent CCS, and which time point is the best to intervene. This would yield important knowledge for establishing guidelines for reducing risk of CVD in future adolescent CCS.

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Paper I

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Device-measured Physical Activity in Adolescent Childhood Cancer Survivors: The PACCS Study

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Abbreviations: BMI: body mass index; CCS: childhood cancer survivors; CNS: central nervous system tumors; cpm: counts per minute; HSCT: hematopoietic stem cell treatment;

ICCC-3: International Classification of Childhood Cancer, third edition; MVPA: moderateto-vigorous physical activity; PA: physical activity; QoL: quality of life; ST: sedentary time.

Article Summary: Worrisome levels of device-measured physical activity and sedentary time in adolescent childhood cancer survivors call for targeted interventions in follow-up care after childhood cancer.

What's Known on This Subject: Physical activity may modify risks of late effects after cancer. The existing knowledge of physical activity and sedentary time in childhood cancer survivors is limited by studies mainly in adult survivors, use of self-reported measures, or small and selected samples.

What This Study Adds: We found low levels of accelerometer-measured physical activity and high levels of sedentary time in a large sample of adolescent childhood cancer survivors. Survivors of CNS tumor had lower physical activity and higher sedentary time compared to the other diagnostic groups.

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Contributors Statement Page

Dr May Grydeland conceptualized and designed the study, designed the data collection instruments, drafted the initial manuscript, and reviewed and revised the manuscript.

Mari Bratteteig carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

Elna Larsen coordinated and carried through data collection, and critically reviewed the manuscript for important intellectual content.

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Drs Corina Rueegg, Hanne Lie, Lene Thorsen, and Profs Sigmund Anderssen and Ellen Ruud conceptualized and designed the study, designed the data collection instruments, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

OBJECTIVES
Physical activity (PA) may modify risks of late effects and improve quality of life after cancer. We aimed to examine levels of PA and sedentary time (ST) in a large, international sample of adolescent childhood cancer survivors in relation to sociodemographic and cancerrelated factors and compare levels of PA and ST to reference cohorts.

METHODS
Survivors from any cancer diagnosis who had completed cancer treatment ≥l year ago, aged

9-16 years, were eligible for the multicenter PACCS (Physical Activity in Childhood Cancer Survivors) study. PA and ST were measured by ActiGraph GT3X accelerometers. We performed linear regression analyses to assess factors associated with moderate-to-vigorous PA (MVPA) and ST, and compared marginal means of total PA, MVPA, and ST in 432 survivors to sex- and age-stratified references (2-year intervals from 8/9-16/17-yearolds) using immediate t-tests for aggregated data.

RESULTS
Among survivors, 34% fulfilled WHO's PA recommendation of ≥60 min of daily MVPA on average, and their ST was 8.7 hours/day. Being female, older, overweight, a survivor of central nervous system tumor, or having experienced relapse were associated with lower MVPA and/or higher ST. Generally, male survivors spent less time in MVPA compared to references, whereas female survivors had similar levels. Both male and female survivors had higher ST than references in nearly all age groups.

CONCLUSION
The low PA and high ST in this large sample of adolescent childhood cancer survivors is worrisome. Combined, our results call for targeted interventions addressing both PA and ST in follow-up care after childhood cancer.

INTRODUCTION

With the growing population of childhood cancer survivors (CCS) at greater risk of premature morbidity and mortality than the general population,[1,2] there is increasing need for preventing treatment-related late effects, such as secondary cancers, cardiovascular diseases, diabetes mellitus, musculoskeletal disorders, fatigue, and reduced quality of life (QoL).[3-6] Pediatric cancer is heterogeneous with more than 100 different entities treated in various ways. Previous research has mainly focused on survivors of acute lymphatic leukemia (ALL), representing about 1/3 of cases. However, ALL-survivors have less late effects than other CCS and are not considered representative for the entire group.[3] Physical activity (PA) and sedentary time (ST) may be two key lifestyle factors influencing the risk of late effects in CCS.[7-9] PA is defined as any bodily movement produced by skeletal muscles that requires energy expenditure, whereas ST is defined as time spent sitting, reclining or lying.[10] In adolescent CCS, observational studies have shown that higher PA and/or lower ST is associated with improved cardiorespiratory and muscular fitness,[11,12] bone health,[13] body composition,[14] and QoL.[15,16] During and immediately after cancer treatment, children and adolescents often have significant impairments in motor performance, potentially affecting their ability to re-engage in PA.[17-19] Exercise training interventions in children with any type of cancer during treatment and/or shortly after treatment have shown to improve functional mobility without increasing the risk of mortality, recurrence, or associated adverse effects.[20] However, knowledge regarding levels of PA and ST in long-term adolescent CCS and whether they return to similar levels as peers after the early phase of survivorship is sparse.[21]

Studies using device-measured PA and ST are lacking in large samples of adolescent CCS. Furthermore, levels have not been compared to population-based norms, and factors associated with low PA and high ST have not been investigated. The current cross-sectional study addresses the lack of knowledge regarding device-measured PA and ST in adolescent CCS and associated factors; basic knowledge that is needed to develop future targeted interventions to mitigate severity of late effects, and to identify those at greatest need of such interventions.

Using the to date largest multicenter European sample of adolescent CCS, the aims of the current study are therefore to:

1) describe levels of device-measured total PA, moderate-to-vigorous PA (MVPA), and ST, stratified by sociodemographic and cancer-related factors,
2) examine sociodemographic and cancer-related factors associated with lower MVPA and higher ST, and
3) compare levels of total PA, MVPA, and ST with age- and sex-stratified references.

METHODS

Study Design

The Physical Activity in Childhood Cancer Survivors (PACCS) study is a multicenter, mixed methods study of CCS from five European countries (Norway, Germany, Denmark, Finland, and Switzerland). The PACCS study is thoroughly described by Lie et al.[22] Below we describe the methods relevant to this cross-sectional sub-study.

Participants

CCS aged 9-16 years with any previous cancer diagnosis, ≥l year post-completion of cancer treatment were eligible. Criteria for exclusion were language difficulties (questionnaires in main native language of each participating country) or limited cognitive function that made it impossible to complete the questionnaire/wear an accelerometer. Participants were recruited during scheduled visits at their follow-up hospital between October 2017 and December 2020.

Physical Activity and Sedentary Time

PA and ST were assessed by accelerometers (ActiGraph GT3X+, ActiGraph LLC, Pensacola, FL), registering acceleration in the vertical axis translated into counts per minute (cpm). The participants received a programmed monitor and were instructed to wear it on the right hip for seven consecutive days during all awake hours, except for swimming and showering. Participants returned the monitor to the study site by postal mail. The accelerometer data was downloaded by the ActiLife software (ActiGraph LLC, Pensacola, FL) at each study site and later uploaded to one common secure server at the Norwegian School of Sports Sciences for processing in the Kinesoft software (version 3.3.80, Loughborough, UK).

We applied two versions of processing the accelerometer data (Supplemental Table 1): 1) the pre-defined “PACCS criteria” that were chosen to best capture the PA behavior of children and adolescents; and 2) the “reference criteria” that reflected the same processing as described for the reference material. We used the PACCS criteria for analyses in CCS only

(aims 1 and 2); and reference criteria when comparing CCS to the references (aim 3). For the PACCS criteria, the accelerometer measured raw signals at 30 Hz summarized in 10-second intervals (epochs), to capture short bouts of PA typically in children.[23] We set non-wear criteria to ≥20 consecutive minutes of zero counts with no interruptions as this is a commonly used non-wear criterion in children.[24] For the reference criteria, we reintegrated accelerometer data into 60-second epochs, and non-wear time was defined as ≥60 consecutive minutes of zero counts, allowing 2 minutes of interruptions.

For both criteria, a valid day was defined as ≥480 minutes/day of wear time. In CCS, we compared total PA (cpm/day) by the number of valid days, adjusted for multiple comparisons (Bonferroni correction), and found no significant differences in total PA by the number of valid days (Supplemental Figure 1). Thus, participants with ≥1 valid day of accelerometer registration were included in our analyses.

We described total PA as the number of cpm, and categorized the activity counts into intensities based on metabolic energy equivalents as ST (<101 cpm), light (101<2296 cpm), moderate (2296<4012 cpm), and vigorous (≥4012 cpm) PA based on the cut-off points proposed by Evenson et al.[25] We calculated the average number of minutes spent per day in each of these intensities. Average minutes per day in MVPA were calculated by summing the time spent in moderate and vigorous PA. Participants were categorized as meeting the World Health Organization's (WHO) recommendation for PA[26] if they engaged in ≥60 minutes of MVPA per day on average.

Demographic and Medical Data

We extracted information on sex, date of birth, height, weight, diagnosis, date of diagnosis, cancer treatment modality (yes/no for chemotherapy, radiation, surgery, hematopoietic stem cell treatment (HSCT)), date of treatment completion, and potential cancer relapse from the participants' medical records. Based on this information, we calculated age at study participation, body mass index (BMI, kg/m^2), age at diagnosis, time since diagnosis, and time since treatment completion. Values of BMI were converted into iso-BMI categories (age- and sex-adjusted values of children' BMI equivalent to adult BMI categories) according to the International Obesity Task Force cut-offs.[27] Diagnoses were based on the International Classification of Childhood Cancer, third edition (ICCC-3) and grouped into leukemias, lymphomas, central nervous system (CNS) tumors, sarcomas, and other tumors

(neuroblastoma, renal tumor, liver tumor, retinoblastoma, germ cell tumor, carcinoma, and "other").[28] Leukemia (acute lymphatic leukemia, acute myeloid leukemia, juvenile myelomonocytic leukemia/myelodysplastic syndrome), lymphoma (Hodgkin's lymphoma and non-Hodgkin's lymphoma), and sarcoma (soft tissue sarcoma, bone tumors), were further divided into subgroups to describe potential differences within these diagnostic groups.

Parents provided information on parental education in an electronic questionnaire.

Reference Material

The reference material consists of pooled and harmonized accelerometer data representing 47,497 individuals (2-18 years) from 18 European countries.[29] We did not have the raw material available, and thus stratified our sample of CCS in accordance to the reference material as sex- and age-stratified (2-year intervals) numbers, marginal means, and standard deviations (SD) of the 8/9 to 16/17-year-olds by contacting the first author to compare total PA, MVPA, and ST to the PACCS data. In the harmonized data, values of total PA were adjusted for country, season, study year, and ActiGraph models. Values of MVPA and ST were additionally adjusted for wear time.

Statistical Analyses

Characteristics of CCS are presented as mean values ± SDs or frequencies with proportions. For 234 of 294 non-participants, we had basic demographic and cancer-related information that we compared to corresponding participants information using t-test for unequal variances.

For aim 1, we described total PA (cpm), MVPA and ST (minutes/day), and proportion meeting the PA recommendation by sociodemographic variables (country, sex, age, iso-BMI, parental education), and cancer-related factors (diagnosis, age at diagnosis, time since diagnosis, relapse). Continuous variables are presented as marginal means ± SDs (calculated from SE*$\sqrt{n}$) adjusted for season and country, and MVPA and ST were additionally adjusted for wear time.

For aim 2, we performed univariable and multivariable linear regression models to examine sociodemographic and cancer-related factors associated with MVPA and ST. MVPA was chosen as the PA outcome in the models, as opposed to total PA, as higher intensity PA is shown to have more consistent and robust relationships with health indicators than PA of lower intensity.[30] Multivariable models included all variables of interest (sex, age, iso-BMI,

parental education, diagnostic group, age at diagnosis, relapse). All univariable and multivariable models were adjusted for country, season, and wear time. We defined missing information on parental education as an own category to avoid losing participants in the analyses. Global P-values for categorical variables were calculated using likelihood-ratio tests. As MVPA and ST have shown to differ by sex and age groups,[29] we tested each association in the multivariable model for interaction with sex and age category (9-11 vs. 1216 years).

For aim 3, we compared marginal means of total PA/MVPA/ST between CCS and references, stratified by sex and age group (2-year interval) using immediate t-tests for unequal variances; a t-test that tests the difference of a variable of interest between two groups based on information of sample size, mean, and SD, if no individual-level data is available.

Statistical analyses were performed in STATA 17 (StataCorp LP, College Station, TX, USA).

Ethics

We collected approvals from the Regional Ethical Committees for Medical and Health Research at all sites and the project owner institution before implementing the project.

Children <16 years provided oral assent, whereas adolescents ≥16 years and guardians provided written consent.

RESULTS

Participants

Of 726 invited CCS, 526 (72%) participated in the study, of which 432 (60%) contributed valid data to the analyses (Figure 1). At study, participants' mean age was 12.2 years (SD=2.2), 48% (n=206) were female, and 64% (n=276) were categorized as normal weight (Table 1). Comparison of participants and non-participants (Supplemental Table 2) showed no differences in basic characteristics, except that participants were slightly younger at study compared to non-participants (12.2 vs. 12.6 years, P=.02).

Physical Activity and Sedentary Time in Childhood Cancer Survivors

On average, participants wore their accelerometer 12.9 hours/day (SD=1.3) for 6.1 days

(SD=1.4). Overall, marginal mean of total PA was 486 cpm, and minutes/day spent in MVPA and ST were 54 and 523, respectively (Table 2). In total, 34% of participants met the PA recommendation.

Descriptive analyses showed that compared to 9-11-year-olds, the 12-16-year-olds had a lower level of total PA (437 vs. 544 cpm), spent less time in MVPA (51 vs. 58 min), were more sedentary (549 vs. 491 min), and a lower proportion (28 vs. 42%) met the PA recommendation (Table 2). Compared to the other diagnostic groups, survivors of CNS tumor had the lowest level of total PA (424 ± 175 cpm/day) and MVPA (46 ± 23 min/day), the highest level of ST (542 ± 58 min/day), and the lowest proportion (17%) meeting the PA recommendation (Table 2, Figure 2).

Factors Associated with Lower MVPA and Higher ST in Childhood Cancer Survivors

Female sex, being overweight, a survivor of CNS tumor, and having experienced relapse were associated with lower MVPA (Table 3). Factors associated with higher ST were; female sex, older age, overweight, and being a survivor of CNS tumor (Table 3).

We found no significant interaction of sex or age category on the association between sociodemographic (sex, age, iso-BMI, parental education) or cancer-related factors

(diagnostic group, age at diagnosis, relapse) and MVPA (all $P_{interaction}>.05$; Table 3). For ST, there were no significant interactions between sex and associated factors, but there was a stronger association between cancer diagnosis and ST in younger survivors (9-11 years) compared to older survivors (12-16 years); Table 3 and Supplemental Figure 2.

Physical Activity and Sedentary Time in Childhood Cancer Survivors Compared to References

On average, references wore their accelerometer for 5 days (SD=1.7) with 12.9 hours of daily wear time (SD=1.7). Using reference processing criteria, male survivors had lower total PA than references in three of five age groups; 8-9 years (523 vs. 633 cpm, P=.003), 12-13 years (490 vs. 559 cpm, P=.005), and 14-15 years (432 vs. 483 cpm, P=.03) (Figure 3A). Also, male survivors spent less time in MVPA at all ages (8-9-year-olds: 42 vs. 61 min, P<.001; 10-11-year-olds: 54 vs. 61 min, P=.05; 12-13-year-olds: 48 vs. 56 min, P=.02; 14-15-yearolds: 44 vs. 50 min, P=.04), except for 16-17-year-olds (Figure 3C). Both total PA and MVPA were similar between female survivors and references in all age groups (Figure 3B and 3D). Both male and female survivors accumulated more ST than references reaching statistical significance for some of the age groups; in male 8-9-year-olds (402 vs. 356 min,

P=.002), 12–13-year-olds (443 vs. 416 min, P=.005), and 14-15-year-olds (489 vs. 471 min, P=.04), and in female 8-9-year-olds (396 vs. 367 min, P=.02), 10-11-year-olds (416 vs. 400 min, P=.03) and 16-17-year-olds (533 vs. 492 min, P=.009); Figure 3E-F.

In Supplemental Figure 3A-F, we display the results in survivors also using the PACCS criteria. The different processing criteria had little influence on total PA, however, the PACCS criteria yielded ~10 minutes more in MVPA and ~60-90 minutes more in ST compared to the reference criteria.

DISCUSSION

Main Findings

Within this international sample of adolescent CCS, we found that only a third of the participants reached WHO's PA recommendation and that CCS spent most of their day sedentary. Factors associated with both less MVPA and/or more ST were being female, older, overweight, having had a diagnosis of CNS tumor, or a relapse. Comparing CCS to references, we found that male survivors were less physically active (both total PA and MVPA), whereas female survivors had equally low levels of PA. Importantly, male and female survivors in all age groups registered more ST than references. As "every minute counts",[10] these differences in PA and ST may be considered clinically meaningful.

Physical Activity and Sedentary Time in Childhood Cancer Survivors

The expected lower levels of total PA and MVPA, and higher ST in female compared to male survivors are in line with previous findings.[31,32] Differences in PA levels between sexes have been discussed by Caru and Curnier (2020), highlighting that parents less often encourage female than male survivors to be physically active, and accept a sedentary lifestyle more often in female compared to male survivors.[33] Cultural and socio-demographic factors were found to influence MVPA levels in adult CCS,[34] and substantial country and region-specific differences in MVPA and ST were found in European youth.[29] These issues may be even more pronounced in some cultural groups.

Age was negatively associated with MVPA, but not after adjusting for other factors. In contrast, age remained positively associated with ST when adjusting for other factors. In adolescent CCS, the existing knowledge concerning the relationship between age and MVPA/ST is limited, but our results align with results from the general population; namely that levels of total PA and MVPA decrease during adolescence, while ST increases.[29,35,36] Reasons for these changes are not clear but factors like less facilities perceived suitable or

accessible, lack of time, increasing autonomy, less social support from family and peers have been suggested as reasons in non-cancer youth samples.[35,37]

Being overweight was associated with lower MVPA and higher ST. This is in line with evidence from the general population, linking device-measured MVPA to adiposity in children and adolescents.[26,38] The current literature on ST and adiposity in the general population is more limited,[39] but sedentary behaviors, especially screen time, have been linked to unfavorable measures of adiposity.[26,39] Our results contrast Schindera et al. who found no association between iso-BMI and meeting PA or screen time recommendations in childhood and adolescent CCS.[40] However, their dichotomization of PA and screen time may have led to loss of power in finding an association between iso-BMI and PA/screen time. Importantly, weight status was the only factor that we examined that is modifiable. If we assume a directional association between iso-BMI and MVPA/ST, helping overweight CCS to do more MVPA may also counterbalance ST and yield synergic improvements to their health, which is important in this population at high long-term risk of cardiovascular disease.[41,42]

Methodologically robust descriptions of MVPA and ST in adolescent survivors of CNS tumor are sparse, which emphasizes the significance of our findings. We found lower levels of MVPA and higher ST in this vulnerable diagnostic group compared to the other diagnostic groups. Moreover, cancer relapse was associated with lower MVPA. This is in line with Schindera et al. who found that self-reported PA (of any intensity) was lower in survivors with relapse.[40] In sum, our results suggest that sociodemographic variables (age, sex, isoBMI) seem equally important as the cancer-related variables for MVPA and ST. However, as the sociodemographic risk factors are similar to those of the general population,[29] clinicians should pay particular attention to the need for PA interventions in CCS of CNS tumor. It has been hypothesized that increments in MVPA is accompanied by increments in ST (PA compensation hypothesis),[43] implicating that ST is not necessarily targeted by increasing MVPA. However, a recent systematic review showed that only six of 22 studies in general youth populations reported evidence of PA compensation, suggesting that one may also reduce ST by focusing on increasing PA.[44] Whether this applies to CCS, who often struggle with late effects from cancer treatment (i.e., fatigue[6]), has not been studied.

Physical Activity and Sedentary Time in Childhood Cancer Survivors Compared to References

Previously published comparisons of device-measured PA between adolescent CCS and controls are few.[45] Using self-reported data, previous studies have shown that adolescent and young adult CCS are less physically active than their siblings or peers.[32,46] Our results support these findings, albeit in male survivors only. The visual impression when comparing male survivors to references might be interpreted as male survivors progress into late adolescence (16/17 years), their levels of total PA, MVPA, and ST align to that of peers. However, the low numbers of male survivors in this age group (n=11) requires careful interpretation. We found similar levels of total PA and MVPA between female survivors and references. Still, female survivors should be targeted to improve PA levels as they were less physically active compared to male survivors. Moreover, as CCS have higher disease risk than the general population, it is important that CCS are at least as physically active as the general population. A recent publication examining barriers and facilitators of PA within a subset of the current population who had various levels of PA (n = 63, mean age 14 years) reported that perceived reduced bodily function, together with fatigue, were barriers to PA, leading to fewer opportunities or less motivation to participate in PA. Moreover, the CCS perceived an ability gap between themselves and their peers that reduced motivation to participate.[47] In contrast, important facilitators were environmental factors such as support from family, peers, and school, and personal factors, such as acceptance, motivation, and goal setting. These are important elements to consider when planning for and designing future PA interventions for CCS.

The addition of the PACCS criteria in Supplemental Figures 3A-F demonstrates that comparing MVPA and ST across studies using different accelerometry processing criteria can lead to biased results and wrong conclusions. The reference data were pooled from several studies with different accelerometer settings and the authors thus analyzed the gathered data based on longer epochs and non-wear time to avoid losing data, however with lower precision. As the nature of PA in children is characterized to be in short sporadic bouts, short epochs (such as 10 sec) are recommended to detect short bursts of high-intensity PA.[23] Until long-awaited consensus on common accelerometer settings in children and adolescents is reached, reporting detailed information about settings used in research studies is crucial.

Strengths and Limitations

A major strength of this study is the relatively large, international sample of adolescent CCS representing different diagnostic groups. The use of accelerometers to assess PA and ST has clear advantages over self-report, which are subject to both recall- and social desirability bias.[48] However, accelerometers have some limitations: they lack ability to detect waterbased activities (e.g., swimming) due to poor water resistance; activities with little vertical acceleration (e.g., cycling); and stationary activities with high load (e.g., resistance training). Also, wearing an activity monitor could change PA behavior. The PACCS criteria for nonwear classification may have underestimated the CCS' time spent sedentary. Aadland et al. compared 10 accelerometer non-wear time criteria, together with logs of non-wear time, in 891 10-year-olds, and reported a 4% and 5% reduction in ST when non-wear criteria were set to 20 minutes versus 45 and 60 minutes of consecutive zeros, respectively.[49] However, this has little impact on association analyses. The study response rate was overall high. Except a slightly older age, there were no differences between participants and non-participants regarding diagnosis, age at diagnosis, or time since diagnosis, supporting the generalizability of our results. However, generalizability is limited to CCS without cognitive impairment and within the same range of age and weight-status. Unfortunately, we lacked detailed treatment information (i.e., specific location or doses of the different treatment modalities) to investigate the impact of treatment burden on MVPA and ST. The cross-sectional study design hinders conclusions on causal relationships of the results, but the data form an important basis for future much-needed prospective and tailored intervention studies in this population.

CONCLUSIONS

As CCS are already at greater risk of premature morbidity and mortality than the general population, adding the negative health impacts of low PA and high ST may further exacerbate the risk of premature morbidity and mortality in CCS. Clinicians and healthcare personnel should have the demonstrated low levels of PA and high ST in mind when addressing follow-up care for CCS, especially in survivors of CNS tumors.

As adolescence is a crucial time period with respect to establishing lifestyle habits, we call for tailored interventions to increase PA and reduce ST in adolescent CCS.

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Figures and Tables

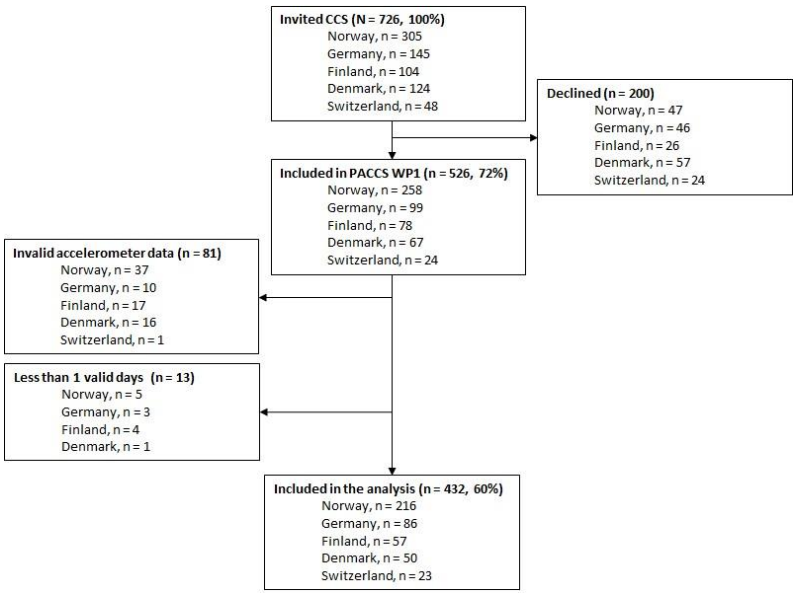


Figure 1: Flowchart of the Inclusion Process in PACCS

Abbreviations: CCS, childhood cancer survivors; PACCS, Physical Activity and fitness in Childhood Cancer Survivors; WP, work package

Table 1: Characteristics of Adolescent Childhood Cancer Survivors in PACCS (n = 432)

Socio-demographic characteristics	N (%) or Mean ± SD
Country	
Norway	216 (50%)
Germany	86 (20%) 57
Finland	(13%)
Denmark	50 (12%)
Switzerland	23 (5%)
Sex	
Male	226 (52%) 206
Female	(48%)
Age at study (years)[a]	12.2 ± 2.2
9-11 years	196 (45%) 236
12-16 years	(55%)
Height (cm)	153 ± 14
Weight (kg)	47.4 ± 14.3
Iso-BMI category	
Underweight	35 (8%)
Normal weight	276 (64%)
Overweight	99 (23%)
Obese	22 (5%)
Parental education[b]	
9-10 years	41 (12%)
11-13 years	138 (40%)
> 13 years	169 (48%)
Cancer-related characteristics	
ICCC-3 diagnostic group	
I. Leukemia	203 (47%)
II. Lymphomas	47 (11%)
III. CNS tumor	69 (16%)
VIII-IX. Sarcomas[c]	36 (8%)
IV-VII, X-XI Other[d]	77 (18%)
Age at diagnosis (years)	5.1 ± 3.3
0-4 years	233 (54%) 172
5-10 years	(40%)
11-15 years	27 (6%)
Time since diagnosis (years)	7.0 ± 3.3
1-4 years	135 (31%)
5-10 years	239 (55%)
11-15 years	58 (13%)
Treatment	
Chemotherapy	393 (91%)
Surgery	159 (37%)
Radiotherapy	97 (23%) 50
HSCT	(12%)
Autologous	*18 (4%)*
Allogeneic	*32 (7%)*
Relapse	
No	390 (90%)
Yes	42 (10%)

Abbreviations: BMI, body mass index; CNS, central-nervous-system; HSCT, hematopoietic stem cell transplantation.

a: In the age category 9<12 years, two 8-year-olds are included. In the age category 13-16 years, four 17-year-olds are included.

b: Missing information on parental education in 84 participants.

c: Sarcomas include sarcomas in soft tissue (n=22), bone tumors (n=12), eye (n=1), and kidney (n=1)

d: Other diagnoses include neuroblastoma (n=18), renal tumor (n=30), liver tumor (n=4), retinoblastoma (n=14), germ cell tumor (n=2), carcinoma (n=3), and “other” (n=6).

Table 2: Physical Activity and Sedentary Time in Adolescent Childhood Cancer Survivors, Stratified by Socio-Demographic and Clinical Variables.

	N	Total PA (cpm/day) Mean ± SD	MVPA (min/day) Mean ± SD	ST (min/day) Mean ± SD	Meets PA rec.[10] N (%)
Total	432	486 ± 183	54 ± 23	523 ± 58	149 (34)
Country					
Norway	216	501 ± 184	56 ± 23	516 ± 58	79 (37)
Germany	86	433 ± 186	49 ± 23	540 ± 59	22 (26)
Finland	57	522 ± 186	56 ± 23	512 ± 59	21 (37)
Denmark	50	480 ± 183	55 ± 23	529 ± 58	19 (38)
Switzerland	23	463 ± 185	49 ± 24	532 ± 61	8 (35)
Sex					
Male	226 206	508 ± 182	58 ± 23	515 ± 57	97 (43)
Female		462 ± 182	50 ± 23	531 ± 57	52 (25)
Age category at study					
9-11 years	198	544 ± 176	58 ± 23	491 ± 50	84 (42)
12-16 years	234	437 ± 176	51 ± 23	549 ± 50	65 (28)
Iso-BMI category					
Underweight	35	474 ± 184	53 ± 23	536 ± 58	12 (34)
Normal weight	276	508 ± 182	57 ± 22	518 ± 57	107 (39)
Overweight	99	442 ± 185	48 ± 23	529 ± 59	25 (25)
Obesity	22	433 ± 183	48 ± 23	526 ± 58	5 (23)
Parental education[a]					
9-10 years	41	450 ± 198	51 ± 24	537 ± 62	11 (27)
11-13 years	138	483 ± 187	54 ± 24	524 ± 59	52 (38)
> 13 years	169	485 ± 190	54 ± 24	529 ± 60	59 (35)
Diagnostic group					
I. Leukemia	203	482 ± 180	54 ± 22	524 ± 57	75 (37)
ALL	*183*	*486 ± 181*	*54 ± 23*	*521 ± 57*	*67 (37)*
AML	*19*	*447 ± 183*	*50 ± 23*	*544 ± 57*	*8 (42)*
JMML/MDS	*1*	*409 ± 180*	*41 ± 22*	*528 ± 56*	*0 (0)*
II. Lymphoma	47	509 ± 180	58 ± 23	513 ± 57	17 (36)
Hodgkin	*14*	*448 ± 181*	*52 ± 23*	*542 ± 57*	*4 (29)*
Non-Hodgkin	*33*	*534 ± 181*	*61 ± 22*	*501 ± 57*	*13 (39)*
III. CNS tumor	69	424 ± 175	46 ± 23	542 ± 58	12 (17)
VIII-IX. Sarcomas	36	466 ± 180	53 ± 22	524 ± 57	11 (31)
Bone tumors	*12*	*446 ± 183*	*47 ± 23*	*535 ± 58*	*3 (25)*
Soft tissue[b]	*24*	*477 ± 184*	*56 ± 23*	*519 ± 58*	*8 (33)*
IV-VII, X-XI Other cancer[c]	77	547 ± 183	60 ± 23	508 ± 58	34 (44)
Age at diagnosis category					
0-3 years	233	510 ± 182	56 ± 23	514 ± 57	94 (40)
4-7 years	172	461 ± 183	51 ± 23	528 ± 57	49 (28)
8-15 years	27	440 ± 182	53 ± 23	560 ± 57	6 (22)
Time since diagnosis category					
1-4 years	135	466 ± 183	52 ± 23	526 ± 56	38 (28)
5-10 years	239	509 ± 182	56 ± 23	512 ± 56	93 (39)
11-16 years	58	438 ± 183	52 ± 23	558 ± 56	18 (31)

Relapse					
No	390	491 ± 183	55 ± 23	521 ± 58	141 (36)
Yes	42	437 ± 184	48 ± 23	532 ± 58	8 (19)

Abbreviations: ALL, acute lymphatic leukemia; AML, acute myeloid leukemia; BMI, body mass index; CNS, central nervous system; cpm, counts per minute; JMML, juvenile myelomonocytic leukemia; MDS, myelodysplastic syndrome; MVPA, moderate-to-vigorous physical activity; PA, physical activity; Rec, Recommendations >60 min MVPA/day; ST, sedentary time.

Note: Results on cpm are adjusted for season and country, results on MVPA and ST are additionally adjusted for wear time.

a: Missing information on parental education in 84 participants.

b: Including 1 kidney sarcoma and 1 eye sarcoma.

c: Other diagnoses include neuroblastoma (n=18), renal tumor (n=30), liver tumor (n=4), retinoblastoma (n=14), germ cell tumor (n=2), carcinoma (n=3), and "other" (n=6).

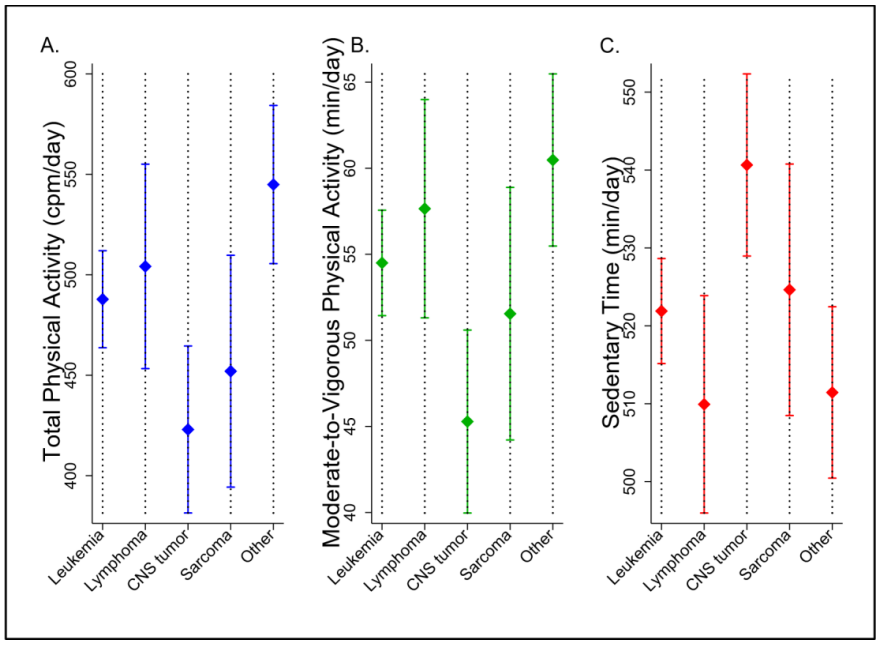


Figure 2: Marginal Means (Diamonds) with 95% Confidence Intervals (Whiskers) for A. Total Physical Activity, B. Moderate-to-Vigorous Physical Activity, and C. Sedentary Time in Adolescent Childhood Cancer Survivors, Stratified by Diagnostic Group (n = 432).

Abbreviations: cpm, counts per minute; CNS, central nervous system; Other, other cancer diagnoses (includes neuroblastoma (n=18), renal tumor (n=30), liver tumor (n=4), retinoblastoma (n=14), germ cell tumor (n=2), carcinoma (n=3), and "other" (n=6)).

Note: The models are adjusted for age, sex, country, and season. Analyses on MVPA and ST are additionally adjusted for wear time.

Table 3: Factors Associated with A. Moderate-to-Vigorous Physical Activity (min/day) and B. Sedentary Time (min/day) in Adolescent Childhood Cancer Survivors (n = 432)

	Univariable regression[a]			Multivariable regression[b]				
A. Moderate-tovigorous physical activity	**β-coeff**	**95% CI**	**P value[c]**	**β-coeff**	**95% CI**	**P value[c]**	**$P_{interaction}$ with sex**	**$P_{interaction}$ with age**
Sex			**.001**			**<.001**	NA	.512
Male	Ref			Ref				
Female	-7.2	-11.5, -2.9		-8.9	-13.1, -4.6			
Age (years)	-1.2	-2.1, -0.2	**.022**	-1.0	-2.0, 0.1	.066	.352	NA
Iso-BMI category			**.004**			**<.001**	.226	.966
Underweight	-4.1	-12.2, 3.9		-4.0	-11.7, 3.8			
Normal weight	Ref			Ref				
Overweight	-9.1	-14.5, -3.8		-10.5	-15.6, -5.3			
Obese	-9.2	-19.1, 0.7		-9.6	-19.3, 0.1			
Parental education[d]			.882			.986	.473	.333
Low	Ref			Ref				
Middle	2.5	-5.8, 10.9		-0.2	-8.2, 7.8			
High	2.7	-5.7, 11.1		-0.2	-8.3, 7.9			
Missing	3.7	-5.4, 12.8		0.8	-8.0, 9.6			
Diagnostic group			**.003**			**<.001**	.946	.154
I. Leukemia	Ref			Ref				
II. Lymphoma	4.7	-2.5, 11.8		4.9	-2.5, 12.2			
III. CNS tumor	-7.7	-14.0, -1.4		-8.9	-15.1, -2.7			
VIII-IX. Sarcomas	-0.8	-8.9, 7.3		0.3	-7.6, 8.1			
IV-VII, X-XI Other	6.4	0.4, 12.4		5.9	0.1, 11.5			
Age at diagnosis (years)	-0.7	-1.4, -0.1	**.030**	-0.5	-1.2, 0.2	.178	.944	NA
Relapse			.080			**.021**	.421	.930
No	Ref			Ref				
Yes	-6.5	-13.9, 0.8		-8.3	-15.4, -1.2			
B. Sedentary time	**β-coeff**	**95% CI**	**P value[c]**	**β-coeff**	**95% CI**	**P value[c]**	**$P_{interaction}$ with sex**	**$P_{interaction}$ with age**
Sex			**.003**			**<.001**	NA	.455
Male	Ref			Ref				
Female	16.6	5.7, 27.5		19.5	10.2, 28.9			
Age (years)	13.4	11.3, 15.6	**<.001**	13.0	10.8, 15.3	**.001**	.476	NA
Iso-BMI category			.173			**.004**	.128	.946
Underweight	17.9	-2.6, 38.4		13.1	-4.1, 30.2			
Normal weight	Ref			Ref				
Overweight	11.2	-2.4, 24.7		19.5	8.1, 30.9			
Obese	7.7	-17.7, 33.1		14.4	-6.9, 35.8			

Parental education[d]			.104			.641	.473	.142
Low	Ref			Ref				
Middle	-10.9	-31.8, 10.1		-1.4	-19.0, 16.2			
High	-5.4	-26.5, 15.8		3.8	-14.0, 21.7			
Missing	-22.5	-45.3, 0.4		-3.7	-23.2, 15.7			
Diagnostic group			**.007**			**.001**	.946	**.017**
I. Leukemia	Ref			Ref				
II. Lymphoma	-10.4	-28.5, 7.8		-15.9	-32.1, 0.3			
III. CNS tumor	18.1	2.1, 34.0		17.6	3.9, 31.2			
VIII-IX. Sarcomas	0.9	-19.6, 21.3		-1.4	-18.8, 16.0			
IV-VII,X-XI Other	-16.0	-31.3, -0.8		-10.5	-23.4, 2.4			
Age 9-11 years						***<.001***		
Leukemia				Ref				
Lymphoma				-31.7	-55.7, -7.6			
CNS tumor				34.7	13.1, 56.3			
Sarcomas				-4.4	-31.9, 23.2			
Other				3.2	-13.8, 20.2			
Age 12-16 years						*.059*		
Leukemia				Ref				
Lymphoma				-9.3	-32.3, 13.6			
CNS tumor				-3.1	-22.1, 15.8			
Sarcomas				-5.5	-29.2, 18.1			
Other				-29.4	-49.9, -8.9			
Age at diagnosis (years)	3.6	2.0, 5.2	**<.001**	0.9	-0.7, 2.4	.290	.958	NA
Relapse			.267			.078	.623	.800
No	Ref			Ref				
Yes	10.5	-8.1, 29.1		14.0	-1.6, 29.7			

Abbreviations: β-coeff, beta coefficient; BMI, body mass index; CI, confidence interval; CNS, central nervous system. a: Univariate regression models are adjusted for season, wear time and country.

b: The multivariable regression model includes all variables of interest listed in the table, the model is additionally adjusted for season, wear time and country.

c: Global P value from likelihood ratio test

d: Missing info on parental education in 84 participants

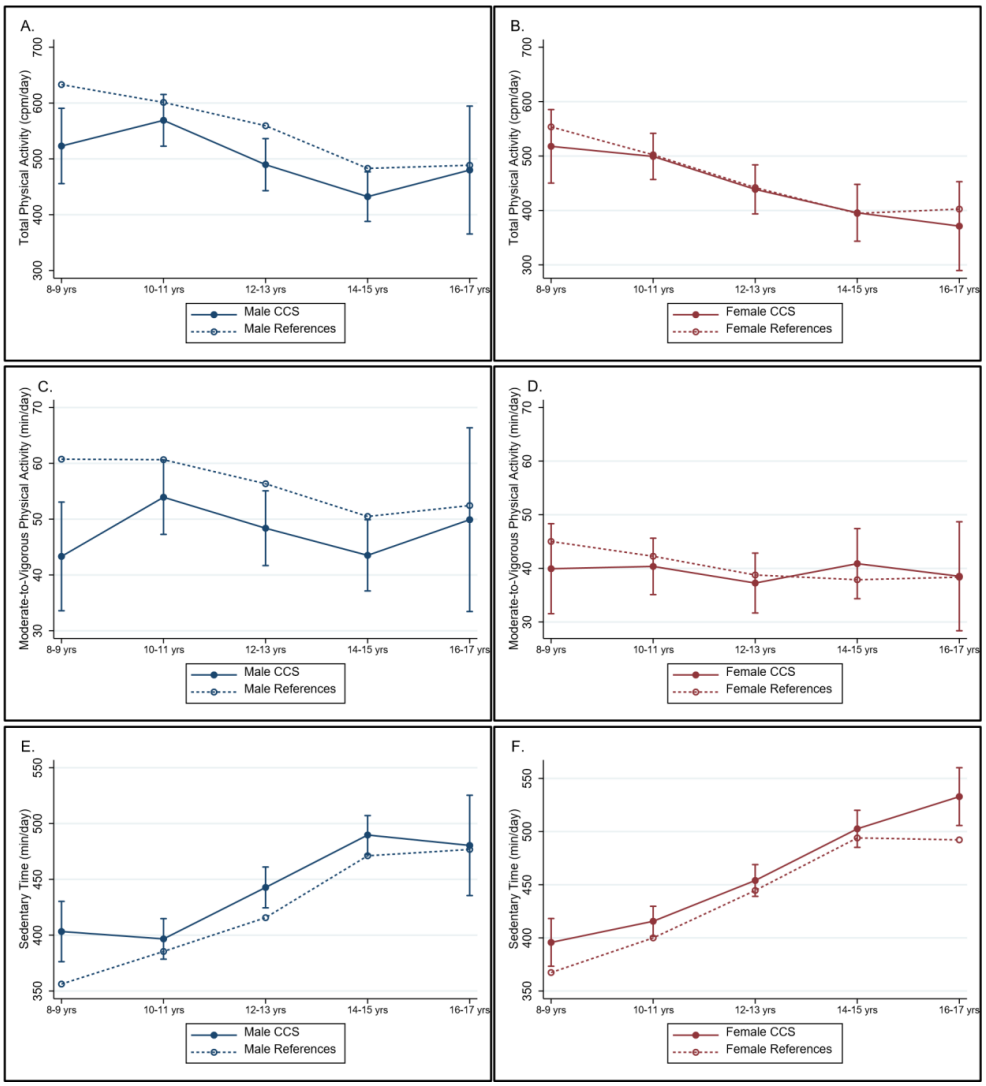


Figure 3: A-B. Total Physical Activity (cpm), C-D. Moderate-to-Vigorous Physical Activity, and E-F. Sedentary Time in Adolescent Childhood Cancer Survivors (Solid Lines, n = 432) and References[29] (Dashed Lines), Stratified by Sex and Age Category*. Dots Represent Marginal Means and Whiskers Represent 95% Confidence Intervals.

Abbreviations: CCS, childhood cancer survivors; cpm, counts per minute; n, number.

Notes: Graphs represent cross-sectional data (connective lines for visual purposes only). Analyses are adjusted for country and season.

Analyses on moderate-to-vigorous physical activity and sedentary time are additionally adjusted for wear time.

*In the age category 8-9 years, only two 8-year-old CCS are included. In the age category 16-17 years, only four 17-year-old CCS are included. Female CCS, n = 206; Male CCS, n = 226.

Supplemental Tables and Figures

Supplemental Table 1: Processing criteria for the accelerometer analyses in the current study. [Online only]

	PACCS criteria	**Reference criteria**
Epoch length	10-sec	60-sec
Non-wear time (consecutive zeros:interruption)	20:0 min	60:2 min
Valid day criteria	≥ 480 min	≥ 480 min
Number of valid days to be included in the analyses	1 day	1 day
Cut-off points*	Evenson	Evenson

* Evenson KR, Mota J. Progress and future directions on physical activity research among youth. J Phys Act Health. Feb 2011;8(2):149-51.

Supplemental Table 2: Basic characteristics of participants and non-participants in the study as numbers (%) or mean ± SD. [Online only]

	Participants n = 432	**Non-participants n = 234[a]**	**P-value**
Sex			0.365
Male	226 (52%)	131 (56%)	
Female	206 (48%)	103 (44%)	
Age at study, years[b]	12.2 ± 2.2	12.6 ± 2.2	**0.024**
Age at diagnosis, years[c]	5.1 ± 3.3	5.1 ± 3.4	0.942
Time since diagnosis, years[c]	7.0 ± 3.3	7.6 ± 3.4	0.069
Time since treatment, years[d]	5.5 ± 3.2	5.8 ± 3.3	0.299
Diagnostic group[e] I.			0.109
Leukemia	203 (47%)	85 (40%)	
III. CNS tumor	69 (16%)	35 (17%)	
II, IV-XII. Tumor outside CNS	160 (37%)	90 (43%)	

Abbreviation: CNS, central-nervous-system; n, number.

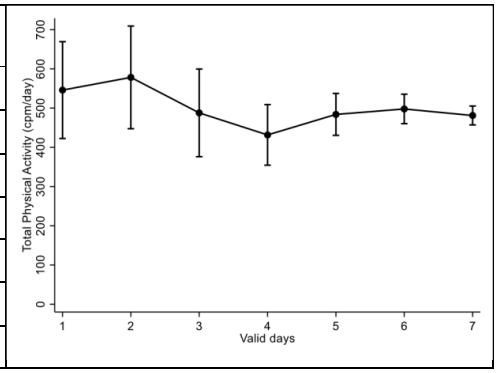
a: Non-participants consisted of those who declined, those with invalid accelerometer data or <1 valid day of accelerometer wear. Missing information on 60 non-participants.

b: Missing information on age at inclusion in 23 non-participants.

c: Missing information on age at diagnosis and time since diagnosis in 70 non-participants. d: Missing information on time since treatment in 4 participants and 70 non-participants.

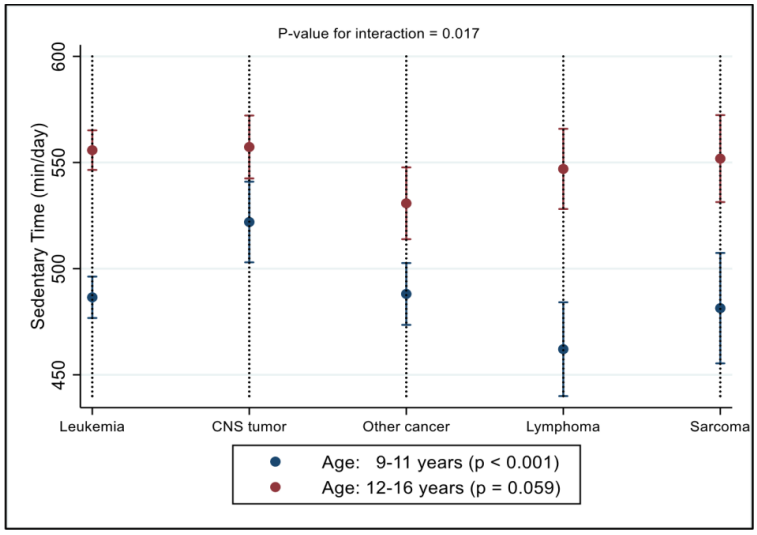
e: Missing information on diagnosis in 24 non-participants.

Valid day(s)	n	Mean cpm/day
1	9	546
2	8	578
3	11	488
4	23	431
5	48	484
6	97	498
7	236	481



Supplemental Figure 1: Participants' total physical activity according to the number of valid days (n = 432). Dots represents mean cpm/day and whiskers represents 95% confidence intervals. [Online only]

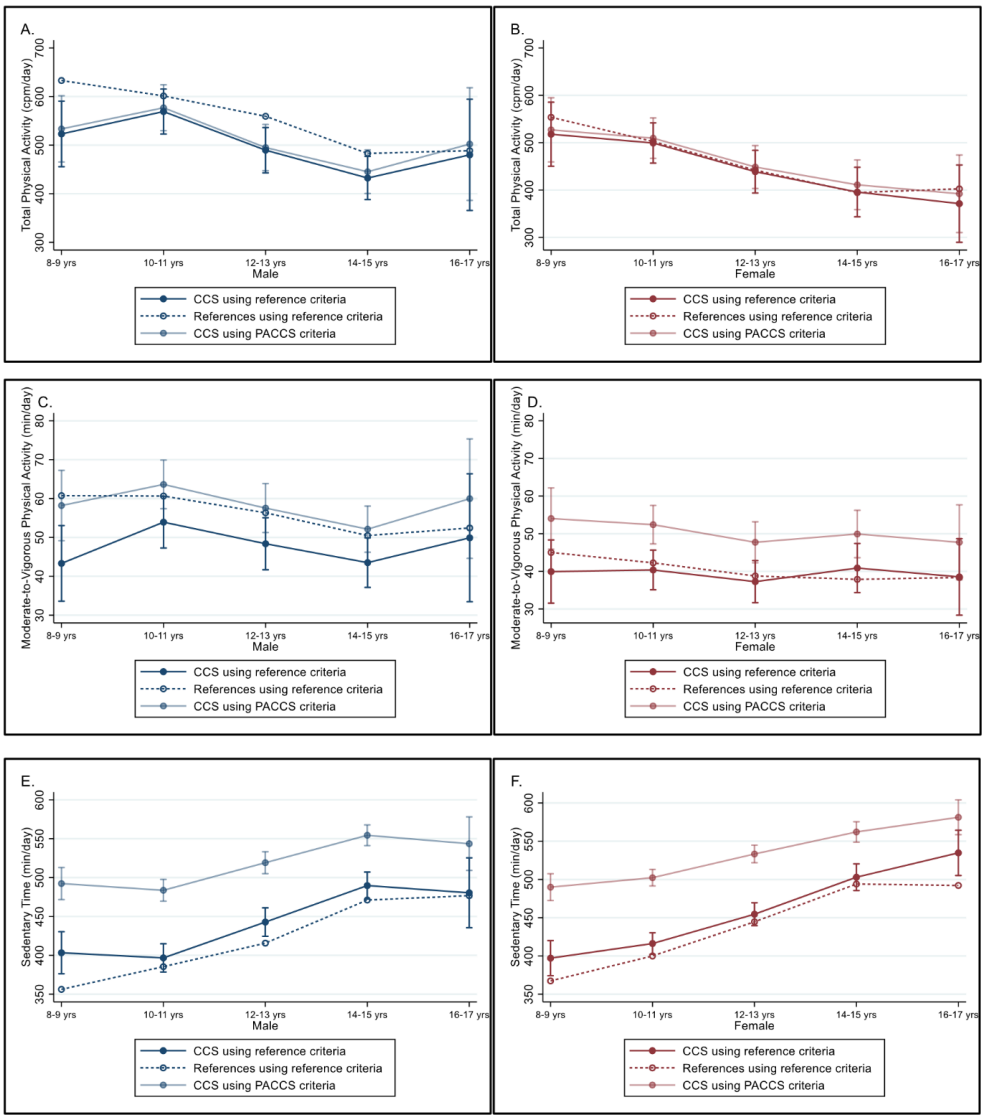
Abbreviation: cpm, counts per minute; n, number.



Supplemental Figure 2: Sedentary time stratified by diagnostic group and age category (n = 432). Dots represents marginal means and whiskers represents 95% confidence intervals. [Online only]

Abbreviation: CNS, central nervous system.

Note: P-values given in legend represents global p-value for the association between diagnostic group and sedentary time for the respective age category.



Supplementary Figure 3: A-B. total physical activity (cpm), C-D. moderate-to-vigorous physical activity, and E-F. sedentary time in adolescent childhood cancer survivors (solid lines, n = 432) and references[40] (dashed line), stratified by sex and age category*. Dots represent marginal means and whiskers represent 95% confidence intervals. [Online only]

Abbreviations: CCS, childhood cancer survivors; cpm, counts per minute.

Notes: Graphs represent cross-sectional data (connective lines for visual purposes only). Analyses are adjusted for country and season.

Analyses on moderate-to-vigorous physical activity and sedentary time are additionally adjusted for wear-time.

*In the age category 8-9 years, only two 8-year-old CCS are included. In the age category 16-17 years, only four 17-year-old CCS are included. Female CCS, n = 206; Male CCS, n = 226.

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Device-measured physical activity and cardiovascular disease risk in adolescent childhood cancer survivors. A physical activity in childhood cancer survivors (PACCS) study

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Objectives: We aimed to compare cardiovascular disease (CVD) risk factors in childhood cancer survivors (CCS) with age- and sex-stratified reference material and examine the association between physical activity (PA) intensities and CVD risk factors in CCS.

Materials and methods: Within the cross-sectional, multicenter *Physical Activity in Childhood Cancer Survivors* (PACCS) study, we collected data on CVD risk factors [VO_{2-peak} ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$), body mass index (BMI, kg/m^2), systolic blood pressure (SBP, mmHg), and total-cholesterol/HDL-cholesterol (Total/HDL)] among CCS aged 9–18 years. CVD risk factors were compared to references with immediate *t*-tests. We transformed CVD risk factors into *z*-scores based on international references and generated an individual CVD risk score: [inverse ZVO_{2-peak} + Z_{BMI} + Z_{SBP} + $Z_{Total/HDL}$)/4]. Multivariable mixed linear regression models were used to analyze the associations between device-measured PA intensities and CVD risk factors.

Results: We included 157 CCS aged on average 13.4 years at inclusion and 8.2 years from diagnosis. Male CCS had lower VO_{2-peak} compared to references (45.4 vs. 49.4 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$, $P = 0.001$), higher diastolic BP (67 vs. 63 mmHg, $P < 0.001$), lower HDL (1.35 vs. 1.44 mmol/L, $P = 0.012$), as well as a tendency to higher CVD risk score (*z*-score=0.14 vs. 0.00, $P = .075$). Female

CCS' CVD risk factors were comparable to references. Vigorous-intensity PA (VPA) was associated with CVD risk factors. A 10-min increase in VPA was associated with higher VO_{2-peak} (β = 4.9, 95% CI, 2.1–7.7), lower Total/HDL (β = −0.3, 95% CI, −0.6 to −0.1) and a lower CVD risk score (β = −0.4, 95% CI, −0.6 to −0.2).

Conclusion: Male adolescent CCS had less favorable values of CVD risk factors compared to references. VPA in adolescent CCS is associated with clinically meaningful favorable values of CVD risk factors.

KEYWORDS

cardiovascular disease risk, cardiometabolic risk, physical activity, accelerometry, childhood cancer survivors

Introduction

Due to major improvements in childhood cancer management, 5-year survival rates have increased to > 80% for children and adolescents diagnosed after the millennium (1–3). However, survival comes at a cost; due to intensive treatment during development and growth, childhood cancer survivors (CCS) are at particularly high risk of developing disease and treatment-related late effects that can interfere with physical and mental health, social functioning, and quality of life (4–6). Cardiovascular disease (CVD) risk factors, such as low cardiorespiratory fitness (CRF), adiposity, and abnormal glucose and lipid metabolism are important late effects among CCS associated with premature mortality in adulthood (7). Notably, CCS may face a sevenfold increased risk of cardiac mortality 30 years after diagnosis compared to age- and sex-matched references (8).

In children and adolescents with no history of cancer, physical activity (PA) is favorably associated with single and clustering of CVD risk factors (9–11). The same beneficial effects of PA on CVD risk is seen among adult CCS, and is therefore proposed as a strategy for secondary prevention and treatment (12–14). However, the relationship between PA and CVD risk in young CCS has not yet been thoroughly investigated, and existing studies are limited by small sample sizes and/or subjective measurement methods (15–21). Subjective measurement methods, such as questionnaires, are prone to measurement errors due to biases such as recognition-, memory- and social desirability (22), and have shown to be unreliable in pediatric populations (23). Existing studies suggest that there is an association between PA and body composition in adolescent CCS also. However, associations with other CVD risk factors remain uncertain. The objectives of this study were thus to compare CVD risk factors in adolescent CCS with age- and sex-stratified references and examine the association between device-measured PA intensities and CVD risk in adolescent CCS. We hypothesized that higher volume and higher intensity of PA are associated with a favorable CVD risk profile in CCS.

Materials and methods

Study design

This study is part of the international, cross-sectional, multicenter study *Physical Activity in Childhood Cancer Survivors (PACCS)* (24). The PACCS study consists of four work packages (WPs). The current study is based on WP2, which recruited CCS from WP1 from three study sites: Oslo University Hospital, Norway; Haukeland University Hospital, Norway; and University Children's Hospital Basel, Switzerland. Manuals of procedures were developed to ensure standardized data collection across study sites. Participant recruitment and data collection were performed from January 2019 to December 2020.

Participants

Childhood cancer survivors were recruited at their pediatric out-patient clinics when visiting for scheduled follow-up care. Inclusion criteria for the current study (WP2) were participation in WP1, age between 9–18 years, ability to perform a cardio-pulmonary exercise test (CPET), and cancer treatment completed ≥ 1 year prior to recruitment. Participants were excluded if they had language or cognitive difficulties, or a CPET was considered not possible due to physical or cognitive impairments.

We used reference values obtained by Stavnsbo et al. in 2018 as reference material (25). The material includes 5,084 females and 5,133 males aged 6–18 years and we used age- and

sex-stratified reference values of the 9–18-year-olds (n = 5161–9229 in females and n = 5214–9214 in males, depending on the CVD risk factor).

Outcomes: Single cardiovascular disease risk factors and cardiovascular disease risk score

Cardiorespiratory fitness was measured as $VO_{2\text{-peak}}$ ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$) by CPET. Gas exchange was determined by breath-by-breath sampling, averaged over 30-s intervals, through a breathing mask (Hans Rudolph Inc., 2700 series, Kansas City, MO, United States), and $VO_{2\text{-peak}}$ was defined as the highest oxygen uptake during the test and was standardized for body mass. Criteria for aborting the CPET were decreasing systolic blood pressure (SBP) or multiple ventricular extrasystoles during the test. The CPET equipment was volume- and gas calibrated daily to ensure valid measurements, and the tests were performed by a physiotherapist in Bergen and exercise physiologists in Oslo and Basel according to standardized procedures.

In Oslo and Bergen, the CPET was performed by walking and running on a stationary treadmill (Rodby RL2700E, Vänge, Sweden, in Oslo; and Woodway PPS 55 Med, Woodway GmbH, Weil am Rhein, Germany, in Bergen). The breathing mask was connected to a metabolic analyzer (Jaeger Oxycon Pro, Viasys Healthcare GmbH, Hoechberg, Germany, in Oslo; and Jaeger Vyntus CPX, Vyaire Medical GmbH, Hoechberg, Germany, in Bergen). A modified Balke protocol for children was applied (26). Initial workload after habituation to the treadmill was 3 km/h, 4 km/h, and additionally 4% inclination, respectively, for the first 3 min. Thereafter, workload was increased every minute by increasing speed by 1 km/h and inclination by 2% every other minute, respectively. The test was stopped and considered maximal when the participant refused further increase in workload or until subjective exhaustion.

In Basel, the Godfrey cycling protocol was performed using an electronically braked ergometer (Ergoline 800; Pilger, St. Gallen, Switzerland) and a Quark B2 metabolic cart (Cortex MetaLyzer 3B, Leipzig, Germany). Work rate was increased every minute by 15–20 W, depending on participant's height and physical fitness until the minimal cadence of 60 revolutions per minute could not be maintained or subjective exhaustion (27). The CPET protocol was different in Basel due to difference in equipment availability.

Reference values of $VO_{2\text{-peak}}$ were also a combination of treadmill and ergometer cycle tests, where a correction factor of 1.05 was applied for children and adolescents who performed their $VO_{2\text{-peak}}$ test on an ergometer cycle (28). In the current study, $VO_{2\text{-peak}}$ values for participants from Basel were adjusted accordingly.

Systolic and diastolic blood pressure (DBP, mmHg) were measured with an electronic monitor in a seated position after a 5-min rest. Two measurements were performed, and the lowest value was registered.

Body mass was measured non-fasted and in light clothing to the nearest 0.1 kg by a digital scale. Height was measured to the nearest 1 mm by a stadiometer. Body mass index (BMI, kg/m^2) was calculated.

Lipid metabolism was measured as cholesterol [Total-c (mmol/L), high-density lipoprotein cholesterol (HDL-c, mmol/L), ratio between Total-c and HDL-c (Total/HDL), and low-density lipoprotein cholesterol (LDL-c, mmol/L)]. Blood samples were collected in non-fasted state by venous sample in Oslo and Bergen, and by venous or capillary sample in Basel. Samples were analyzed by photometric methods at medical laboratories.

We generated z-scores for all of the above-mentioned single CVD risk factors based on the reference material and followed their guideline published in their **Supplementary material** (25). We first calculated age- and sex-specific reference values based on the published intercepts and beta-coefficients (25). Those reference values were then used to create z-scores based on the following formula: $z\text{-score} = (\text{mean}_{ccs} - \text{mean}_{reference})/\text{SD}_{reference}$. Stavnsbo et al. suggest using (natural) log-transformed values of BMI and Total/HDL to calculate the age- and sex-specific reference values, we thus log-transformed those two variables in our material accordingly. The resulting z-scores were then back-transformed to the original unit of 1 SD for meaningful interpretation (29).

Finally, we calculated a mean continuous CVD risk score = $(\text{inverse}Z_{VO2\text{-peak}} + Z_{BMI} + Z_{SBP} + Z_{Total/HDL})/4$. The CVD risk score was set to missing for participants with < 3 CVD risk factors (n = 1), and were thus omitted from analyses concerning CVD risk score. We calculated a CVD risk score as multiple CVD risk factors have shown to exert a synergetic effect on morbidity and mortality from CVD in later life, as compared to single risk factors (30, 31).

Exposure: Physical activity intensities

A hip-worn accelerometer (ActiGraph GT3X-BT, Pensacola, FL, United States) was used to measure PA. Participants were instructed to wear the monitor for 8 consecutive days and to remove the monitor only for sleep and water-based activities. The accelerometers were initialized at a sampling rate of 30 Hz, and raw files were analyzed at 10-s epoch using the KineSoft analytical software version 3.3.80 (Loughborough, United Kingdom), restricted to hours between 06:00–23:59. Non-wear time was defined as periods of $\geq$ 20 consecutive minutes of zero counts. Minimum wear time of 8 h/day was required for a valid day, and $\geq$ 3 valid days were required

for a person to be included in the analyses (**Supplementary Figure 1**). PA in the number of the participant's valid days was averaged to represent their daily PA. Cut-points derived from counts per minute (cpm) were used to categorize the accelerometry data into light-intensity PA (LPA, 100–1999 cpm), moderate-intensity PA (MPA, 2000–5999 cpm), vigorous-intensity PA (VPA, ≥ 6000 cpm), and moderate-to-vigorous-intensity PA (MVPA, ≥ 2000 cpm), respectively (32–34).

Covariates: Age, sex, puberty stage, parental education, and cancer-related characteristics

Puberty stage was determined by the self-reported Pubertal Development Scale questionnaire assessing indices of pubic hair, voice, and facial hair in males; and pubic hair, breast development, and menstruation in females (35). Participants were categorized as pre-pubertal if the participant reported the lowest category for all indices, post-pubertal if the participant reported the highest category for all indices, whereas the remaining participants were categorized as pubertal. Conversion of the original continuous Pubertal Development Scale into a 3-point ordinal scale is shown to be a reliable and valid tool in the pediatric population (36), albeit we are not aware of any validation studies performed in adolescent CCS.

Six categories for parent-reported parental education were collapsed into three categories: (1) 9–10 years; (2) 11–13 years; and (3) > 13 years.

Cancer diagnosis, and a limited number of available key factors from cancer treatment, that were available in conjunction with recruitment of participants, were extracted from medical records: cumulative anthracycline dose (Doxorubicin isotoxic equivalent dose, mg/m^2) (37), cumulative radiation dose (Gy), and high-dose steroids (yes/no) as part of the cancer treatment protocol. Age at diagnosis and time since diagnosis were calculated.

Statistical analyses

Characteristics of participants are expressed as mean ± SD or frequency (proportion), overall and stratified by sex. Comparisons between male and female CCS were made by Welch's *t*-test for unequal variances for continuous variables, and by Chi square tests for categorical variables.

Comparison of CVD risk factors between CCS and references was performed using immediate *t*-tests with unequal variances. Associations between PA intensities and CVD risk factors were assessed using mixed effects linear regression models with study site as random intercept to account for clusters in the data. To adjust for potential confounding, we added covariates to the model (fixed effects) based on a directed acyclic graph drawn in Dagitty version 3.0[1] (38) (**Supplementary Figure 2**). The following "minimal sufficient adjustment set" was identified: age, sex, puberty stage, parental education, age at diagnosis, time since diagnosis, and cancer treatment.

In the crude model, we adjusted only for the cluster variable study site (Model 1). In multivariable models, we additionally adjusted for age, sex, puberty stage and parental education (Model 2), and cancer-related variables (age at diagnosis, cumulative anthracycline dose, cumulative radiation dose, high-dose steroid treatment; Model 3). Time since diagnosis was omitted in Model 3 due to collinearity with age and age at diagnosis. We performed likelihood-ratio tests (LRT) to compare Model 2 and 3 in order to investigate influence of cancer-related characteristics on the PA-CVD risk factor associations. To compare models with LRT, *n* needs to be identical. Thus, missing parental education was defined as own category in the model and missing information on anthracycline dose (n = 9) and radiation dose (n = 1) was set to zero, avoiding loosing participants in analyses due to missing information on covariates. All *P*-values were two-sided, and we considered *P*-values ≤ 0.05 as statistically significant. Analyses were conducted using Stata statistical software release 16.0 (StataCorp LP, College Station, TX, United States).

Ethics

Physical Activity in Childhood Cancer Survivors WP2 was approved by the Norwegian Regional Committee for Medical Research Ethics (project ID 2018/739), the Data protection Officer at Oslo University Hospital, and the Ethics Committee of North-Western and Central Switzerland (project ID 2019-00410). Written informed consent to participate in the current study was collected from all participants/parents.

Results

Study population

Of the 267 eligible invited CCS, 157 (59%) agreed to participate in the study and were included in descriptive analyses; 137 (51%) participants were included in the regression models (**Figure 1**).

The participants were on average 13.4 years old at inclusion and 8.2 years from diagnosis (**Table 1**). Half of the participants

1 www.dagitty.net

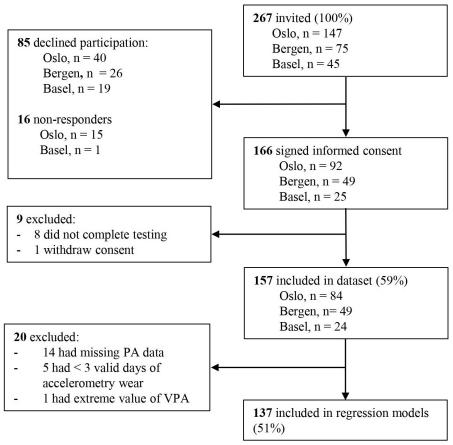

FIGURE 1
Flow chart of the inclusion process in PACCS WP2.

were survivors of leukemia, 78% had received anthracyclines, 29% had received radiotherapy, and 57% had received high-dose steroid treatment as part of their cancer treatment protocol. Females and males were comparable with respect to demographic and cancer-related characteristics, except borderline differences in distribution of puberty stage (18, 73, and 10% of the females were pre-pubertal, pubertal, and post-pubertal, respectively, whereas 27, 70, and 2% of the males were pre-pubertal, pubertal, and post-pubertal, respectively, P_{trend} = 0.077) and proportion experiencing relapse (4% in females vs. 12% in males, P = 0.077).

Basic characteristics were not significantly different between participants and non-participants in WP2 (**Supplementary Tables 1**, **2**), though there was a tendency that fewer participants had experienced relapse compared to non-participants (9 vs. 17%, P = 0.10), and female participants were slightly younger than female non-participants (12.1 vs. 12.9 years, P = 0.11).

Cardiovascular disease risk factors

Male CCS had lower $VO_{2\text{-peak}}$ compared to references [45.4 vs. 49.4 mL·kg^{-1}·min^{-1}, P = 0.001 (**Table 2**)], as well as higher DBP (67 vs. 63 mmHg, P < 0.001) and lower HDL-c (1.35 vs. 1.44 mmol/L, P = 0.012). There were no differences between female CCS and references in any of the CVD risk factors.

Males had a z-score of −0.52 (95% CI, −0.82, −0.22, P = 0.001) for $VO_{2\text{-peak}}$ and 0.14 (95% CI, −0.01, 0.30, P = 0.075) for the CVD risk score (**Figure 2**). Females had a z-score of −0.16 (95% CI, −0.45, 0.12, P = 0.26) for $VO_{2\text{-peak}}$ and 0.02 (95% CI, −0.14, 0.18, P = 0.81) for the CVD risk score.

TABLE 1 Demographic and cancer-related characteristics in adolescent CCS, overall and stratified by sex.

	All (n = 157)	Females (n = 73)	Males (n = 84)	P
Demographic characteristics				
Age at study, years	13.4 ± 2.5	13.2 ± 2.7	13.5 ± 2.4	0.53
Puberty stage				0.077
Pre-pubertal	36 (23)	13 (18)	23 (27)	
Pubertal	112 (71)	53 (73)	59 (70)	
Post-pubertal	9 (6)	7 (10)	2 (2)	
Caucasian ethnicity	146 (93)	68 (93)	78 (93)	0.28
Parental education[a]				0.40
Primary school	6 (6)	3 (8)	3 (5)	
High school	32 (34)	9 (25)	23 (39)	
University or college	57 (60)	24 (67)	33 (56)	
Cancer-related characteristics				
Age at diagnosis, years	5.2 ± 3.4	5.4 ± 3.3	5.1 ± 3.4	0.59
Time since diagnosis, years	8.2 ± 3.6	7.9 ± 3.5	8.4 ± 3.6	0.34
Diagnoses (ICCC-3)				0.25
I Leukemias	78 (50)	39 (53)	39 (46)	
II Lymphoma	16 (10)	4 (5)	12 (14)	
III CNS tumors	18 (11)	7 (10)	11 (13)	
IV–XII other tumors	45 (29)	23 (32)	22 (26)	
Relapse	13 (8)	3 (4)	10 (12)	0.077
Anthracyclines	121 (78)	57 (79)	64 (77)	0.85
Cumulative dose (mg/m^2) (31),[b] (range)	161 ± 90 (45–450)	161 ± 91 (80–450)	161 ± 89 (45–410)	0.82
Radiotherapy	45 (29)	21 (29)	24 (29)	0.98
Cumulative dose (Gy) (range)[c]	33 ± 18 (12–70)	34 ± 20 (12–70)	32 ± 16 (12–54)	0.98
High-dose steroids[d]	90 (57)	42 (58)	48 (57)	0.96

Continuous variables are displayed as mean and standard deviation, categorical variables as frequency and proportion. There are no missing values besides the ones stated in the footnote below. CCS, childhood cancer survivors; CNS, central nervous system; CVD, cardiovascular disease; ICCC-3, International Classification of Childhood Cancer – third edition.
[a]Missing information on parental education for 62 participants.
[b]Missing cumulative anthracycline dose for nine participants.
[c]Missing cumulative radiation dose for one participant.
[d]As part of cancer treatment protocol (yes/no).

Physical activity

In this substudy of PACCS, participants wore their accelerometer, on average, 13 h/day for 6 days. Participants engaged on average in 60 ± 28 min of MVPA/day (**Table 3**).

Associations between physical activity and cardiovascular disease risk factors

The fully adjusted model (Model 3) showed that all PA intensities were associated with $VO_{2\text{-peak}}$, and the coefficients increased in size with higher intensity PA (**Table 4**). A 10-min

TABLE 2 Comparison of single CVD risk factors in CCS vs. references, stratified by sex.

CVD risk factors	Females			Males		
	CCS ($n = 73$)[a]	References (25) ($n = 5161$)[b]	*P*-value	CCS ($n = 84$)[a]	References (25) ($n = 5214$)[b]	*P-value*
$VO_{2\text{-peak}}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	40.1 ± 7.8	41.1 ± 6.6	0.25	45.4 ± 10.8	49.4 ± 7.7	0.001
BMI (kg/m^2)	19.9 ± 3.8	20.0 ± 4.1	0.79	19.8 ± 3.6	20.0 ± 4.0	0.74
ln BMI	2.98 ± 0.18	2.98 ± 0.18	0.99	2.97 ± 0.17	2.97 ± 0.17	0.94
SBP (mmHg)	104 ± 10	105 ± 9	0.55	109 ± 9	109 ± 9	0.75
DBP (mmHg)	63 ± 9	63 ± 8	0.83	67 ± 9	63 ± 8	< 0.001
Total-c (mmol/L)	4.2 ± 0.8	4.3 ± 0.7	0.64	4.0 ± 0.8	4.1 ± 0.7	0.73
HDL-c (mmol/L)	1.47 ± 0.29	1.50 ± 0.32	0.30	1.35 ± 0.30	1.44 ± 0.32	0.012
Total/HDL	3.0 ± 0.8	3.0 ± 0.8	0.75	3.1 ± 0.9	3.0 ± 0.8	0.16
ln Total/HDL	1.06 ± 0.23	1.05 ± 0.24	0.64	1.10 ± 0.28	1.06 ± 0.25	0.15
LDL-c (mmol/L)	2.5 ± 0.8	2.4 ± 0.7	0.058	2.4 ± 0.7	2.2 ± 0.6	0.14

Variables are displayed as mean and standard deviation. BMI, body mass index; CCS, childhood cancer survivors; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein-cholesterol; LDL-c, low-density lipoprotein-cholesterol; ln, natural logarithm; SBP, systolic blood pressure; Total-c, total-cholesterol; VO2-peak, peak oxygen consumption.

[a]CVD risk factors varied from $n = 72$–73 in female CCS and $n = 77$–84 in male CCS.

[b]CVD risk factors varied from $n = 5161$–9229 in female references and $n = 5214$–9214 in male references.

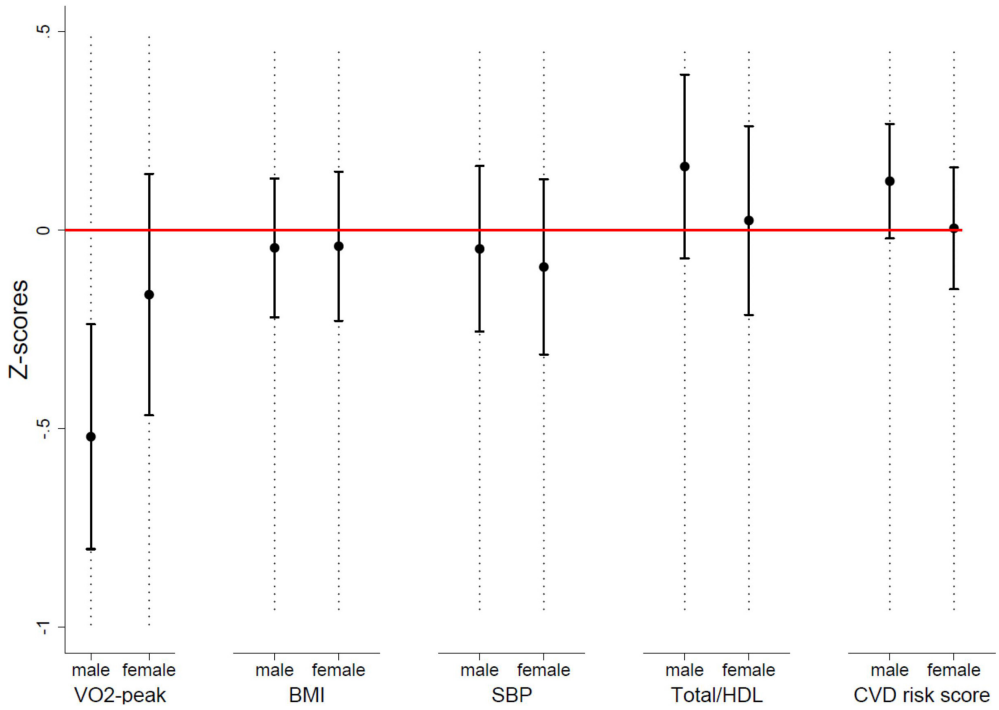

FIGURE 2
Mean *Z*-scores with 95% CI for single CVD risk factors and the CVD risk score, stratified by sex. BMI, body mass index (kg/m^2); CVD, cardiovascular disease; SBP, systolic blood pressure; Total/HDL, total-cholesterol/HDL-cholesterol; VO2-peak, peak oxygen consumption.

increase in LPA, MPA, and VPA was associated with a higher $VO_{2\text{-peak}}$ of 0.5 (95% CI, 0.1–0.8, P = 0.008), 1.0 (95% CI, 0.4–1.6, P = 0.001), and 4.9 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ (95% CI, 2.1–7.7, P = 0.001), respectively. Adding cancer-related variables to the model assessing the association between LPA and $VO_{2\text{-peak}}$ did not alter the strength of the association. However, including cancer-related variables to the model resulted in a significantly better model fit (P_{LRT} comparing models = 0.002). Including cancer-related variables reduced the strength of the association between MPA and $VO_{2\text{-peak}}$ from 1.3 to 1.0 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$; and from 5.6 to 4.9 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ for the association between VPA and $VO_{2\text{-peak}}$ (P_{LRT} comparing models = 0.011 and 0.004 for MPA and VPA, respectively).

Both MPA and VPA were associated with lower Total/HDL (−0.1, 95% CI, −0.1 to −0.0, P = 0.022; and −0.3, 95% CI, −0.6 to −0.1, P = 0.016, respectively), and MPA was additionally associated with lower SBP (-0.9 mmHg, 95% CI, −1.5 to −0.3, P = 0.005). Adding cancer-related variables to the model did not affect the association between PA intensities and Total/HDL or SBP. None of the PA intensities were associated with BMI and including cancer-related variables in the model did not affect the associations.

Also, MPA and VPA were associated with the CVD risk score. A 10-min increase in MPA and VPA were associated with a lower CVD risk score of −0.1 (95% CI, −0.1 to −0.0, $P < 0.001$), and −0.4 (95% CI, −0.6 to −0.2, P = 0.001), respectively. Adding cancer-related variables to the model did not affect the association between PA intensities and the CVD risk score.

Discussion

Main findings

We found that male adolescent CCS had lower $VO_{2\text{-peak}}$ and HDL-c, and higher DBP and CVD risk score compared to references, in contrast to female adolescent CCS where all CVD risk factors were comparable to references. To our knowledge, this is the first study examining the association between device-measured PA and CVD risk factors in adolescent CCS. We found that PA was associated with single CVD risk factors and the CVD risk score.

TABLE 3 Physical activity intensities in adolescent CCS, overall and stratified by sex.

	All (n = 137)	Females (n = 63)	Males (n = 74)
Physical activity			
LPA (min/day)	175 ± 49	172 ± 41	177 ± 55
MPA (min/day)	55 ± 25	52 ± 20	57 ± 29
VPA (min/day)	5 ± 5	5 ± 5	5 ± 5
MVPA (min/day)	60 ± 28	57 ± 23	62 ± 32

Variables are displayed as mean and standard deviation. CCS, childhood cancer survivors; LPA, low-intensity physical activity; MPA, moderate-intensity physical activity; MVPA, moderate-to-vigorous-intensity physical activity; PA, physical activity; VPA, vigorous-intensity physical activity.

Comparison to other studies

Cardiorespiratory fitness

With respect to the single CVD risk factors, we found that PA at any intensity was positively associated with $VO_{2\text{-peak}}$, and higher intensity PA was inversely associated with Total/HDL. MPA was additionally inversely associated with SBP. Our results are in line with a previous study by Jarvela et al. showing a positive association between self-reported PA and $VO_{2\text{-peak}}$ in young adult survivors of acute lymphoblastic leukemia (15).

Adiposity

Our results conflict with previous studies by Slater et al. showing inverse associations between self-reported PA and adiposity in adolescent and young adult CCS (18, 19). These studies used waist circumference, body fat percentage, subcutaneous and visceral adipose tissue as measures of adiposity, and PA was assessed by questionnaire, which might explain the differences in results. This claim is supported by two other studies in CCS: Tonorezos et al. found an inverse association between device-measured PA and body fat percentage, but not with BMI, in young adult CCS (21); Jarvela et al. found that an increase in PA led to reduced adiposity, measured as waist circumference, waist-to-hip ratio, and body fat percentage, but not with BMI (15). Thus, BMI does not seem like an appropriate measure of adiposity in CCS to detect a potential association with PA. BMI does not distinguish between fat mass and fat-free mass, and studies in CCS have shown that despite having similar BMI z-score as healthy controls, they have deficits in fat-free mass and excesses of fat mass (39).

Blood pressure and lipid metabolism

Jarvela et al. additionally found that an increase in PA resulted in lower SBP and higher HDL-c (15). Our results are in line with these findings. We did not look at the association between measures of PA and HDL-c separately. However, we found an inverse association between PA and ratio of Total/HDL, which might be explained by higher HDL-c. Other cross-sectional studies in CCS have failed to detect these associations (18, 19, 21). This might be due to methodological differences in measuring PA.

Influence of cancer treatment on the association between physical activity and cardiovascular disease risk factors

A recent study by Schindera et al. found a strong association between CRF and CVD risk factors in young adult

TABLE 4 Associations between 10-min increase in PA intensities and CVD risk factors in adolescent CCS.

	10 min LPA (n = 137)			10 min MPA (n = 137)			10 min VPA (n = 137)		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
	β -coefficients with 95% CIs								
$VO_{2\text{-peak}}$ ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$)[a]	0.4 (0.0 to 0.7)	0.5 (0.1 to 0.8)	0.5 (0.1 to 0.8)	1.2 (0.6 to 1.8)	1.3 (0.7 to 1.9)	1.0 (0.4 to 1.6)	5.5 (2.5 to 8.6)	5.6 (2.6 to 8.5)	4.9 (2.1 to 7.7)
BMI (kg/m^2)	−0.2 (−0.3 to −0.1)	−0.1 (−0.2 to 0.1)	−0.0 (−0.2 to 0.1)	−0.3 (−0.5 to −0.0)	−0.1 (−0.3 to 0.1)	−0.1 (−0.3 to 0.2)	−1.1 (−2.3 to 0.2)	−0.8 (−2.0 to 0.3)	−0.8 (−2.0 to 0.3)
SBP (mmHg)[a]	−0.5 (−0.8 to −0.1)	−0.1 (−0.5 to 0.3)	−0.1 (−0.5 to 0.2)	−1.0 (−1.6 to −0.3)	−0.8 (−1.4 to −0.2)	−0.9 (−1.5 to −0.3)	−2.2 (−5.7 to 1.2)	−1.8 (−5.0 to 1.3)	−2.0 (−5.1 to 1.2)
Total/HDL[b]	−0.0 (−0.1 to 0.0)	−0.0 (−0.0 to 0.0)	−0.0 (−0.0 to 0.0)	−0.1 (−0.1 to −0.0)	−0.1 (−0.1 to −0.0)	−0.1 (−0.1 to −0.0)	−0.4 (−0.7 to −0.1)	−0.3 (−0.6 to −0.1)	−0.3 (−0.6 to −0.1)
CVD risk score[c]	−0.0 (−0.0 to 0.0)	−0.0 (−0.1 to 0.0)	−0.0 (−0.1 to 0.0)	−0.1 (−0.1 to −0.0)	−0.1 (−0.1 to −0.0)	−0.1 (−0.1 to −0.0)	−0.4 (−0.6 to −0.1)	−0.4 (−0.6 to −0.2)	−0.4 (−0.6 to −0.2)

BMI, body mass index; CCS, childhood cancer survivors; CVD, cardiovascular disease; LPA, low-intensity physical activity; MPA, moderate-intensity physical activity; PA, physical activity; SBP, systolic blood pressure; Total/HDL, ratio of total-cholesterol and high-density lipoprotein-cholesterol; VO2-peak: peak oxygen consumption; VPA, vigorous-intensity physical activity. Adjustments: Model 1 is adjusted for site; Model 2 is additionally adjusted for age, sex, puberty stage, and parental education; Model 3 is additionally adjusted for age at diagnosis, cumulative anthracycline dose, radiation dose, and high-dose steroid treatment (yes/no).

[a]Missing information on VO2-peak (unknown reason) and SBP in two participants.

[b]Missing information on Total/HDL in six participants.

[c]CVD risk score was set to missing for one participant due to < 3 CVD risk factors.

CCS (40). They report that the associations did not change noticeably when adjusting the analyses for cancer treatment. They suggested that survivors may have modified their CVD risk through CRF. Our statistical models were similar, where we compared the associations with- and without including treatment variables as confounders. We found that cancer-related variables reduced the strength of the association between PA and $VO_{2-peak,}$ which might indicate that CCS have smaller increase in $VO_{2\text{-peak}}$ in response to PA than adolescents with no history of cancer. Some potential mechanisms induced by cancer treatment, may be that cardiovascular diseases limit performance during exercise through impairments in systolic and diastolic function, or heart rate response; pulmonary limitations may cause impairments in ventilation and gas exchange; and arterial stiffness and endothelial dysfunction may limit the vascular system (41). We found no impact of cancer-related variables on the association between PA and the other CVD risk factors, suggesting that PA is associated with SBP and Total/HDL independently of former cancer treatment.

Strengths and limitations

The strengths of this study are the inclusion of adolescent CCS, and the use of reliable and valid measurement methods, including device-measured PA and directly measured $VO_{2\text{-peak}}$. We also had access to some key cancer-related characteristics, enabling us to adjust for them in the analyses. Moreover, we recruited participants with a history of various childhood cancer diagnoses. Most previous studies have included participants with a history of acute lymphoblastic leukemia, only. This study has also limitations to be considered. Our analyses assume directional associations, however, associations of cross-sectional data have no real direction. We were thus unable to draw any causal inference due to the cross-sectional design. We did not have fasted blood sample values as the references did. However, Total-c and HDL-c are mainly unaffected by fasted state (42). Moreover, the use of BMI as a measure of adiposity might have reduced the possibility to find an association between PA and adiposity. Self-reporting of puberty stage might be prone to bias, however, a recent study found substantial agreement between Pubertal Development Scale and Tanner stage when each scale was combined into three categories (36), as we did. We failed in finding reference material for HbA1c, and we were thus unable to compare a measure of glucose metabolism, which is a central CVD risk factor, in CCS to references. Lastly, the relatively low inclusion rate (59%) might reflect that an invitation to participate in a study with physical performance testing might appeal more to those who are regularly physically active and may thus have led to selection bias. Even though of no statistical difference, our analysis of non-participants showed that those who had experienced relapse, and females of higher age, were less likely to participate in the current study (WP2).

Conclusion

We found that male adolescent CCS had less favorable values of CVD risk factors compared to references. Moreover, we found higher levels of PA to be associated with a more favorable CVD risk profile in adolescent CCS. This highlights the need to encourage and help adolescent CCS to increase or

maintain their PA level. Whether higher CVD risk is due to lower PA level is yet to be determined. Randomized controlled trials or cohort studies are needed to explore whether increased PA can reduce CVD risk in adolescent CCS.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The study was reviewed and approved by the Regional Committee for Medical and Health Research Ethics (2018/739). Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

Author contributions

MB: formal analysis, investigation, methodology, visualization, writing original draft, and writing – review and editing. SA: conceptualization, funding acquisition, methodology, project administration, supervision, visualization, and writing – review and editing. CR: methodology, supervision, validation, visualization, and writing – review and editing. ER: conceptualization, funding acquisition, project administration, supervision, and writing – review and editing. IT and SK: investigation and writing – review and editing. MG: conceptualization, funding acquisition, investigation, methodology, project administration, supervision, and writing – review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.977365/full#supplementary-material

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Supplementary Material

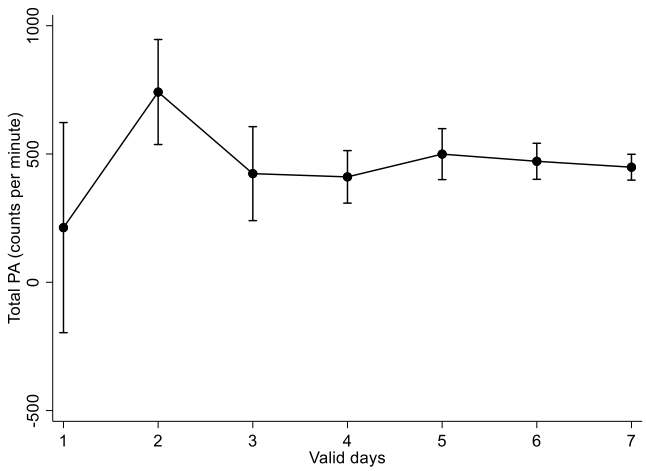

Figure 1: Margins plot showing participant's total physical activity (mean counts per minute/day with 95% CI) according to their respective number of valid days (n = 143)

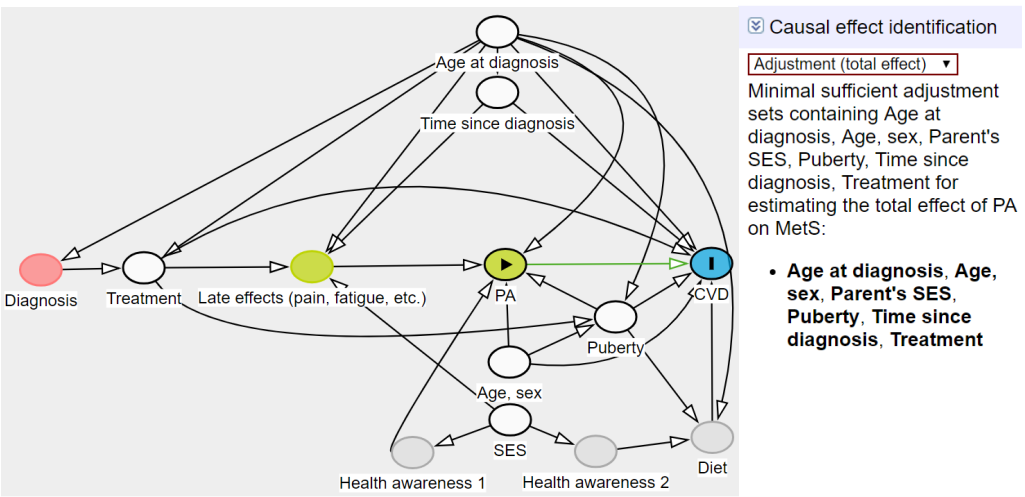

Figure 2: Directed acyclic graph created in *Dagitty*

Abbreviations: CVD, cardiovascular disease (risk factors); PA, physical activity; SES, socioeconomic status

Table 1: Key characteristics of non-participants and participants in PACCS WP2

	Non-participants (n = 89)[a]	Participants (n = 157)	P
Sex			.81
Girls	40 (45)	73 (47)	
Boys	49 (55)	84 (54)	
Age at inclusion in WP1, years[b]	12.4 ± 2.2	12.1 ± 2.2	.30
Age at diagnosis, years[c]	5.1 ± 3.1	5.1 ± 3.4	.93
Time since diagnosis in WP1, years[d]	7.1 ± 3.2	6.8 ± 3.2	.56
Diagnosis (ICCC-3)			.96
I. Leukemia	43 (48)	78 (50)	
II. Lymphoma	11 (12)	16 (10)	
III. Tumor CNS	10 (11)	18 (11)	
IV-XII Tumor other	25 (28)	45 (29)	
Relapse	15 (17)	14 (9)	.10

Note: Values are based on data extracted from medical records prior to recruitment to PACCS WP1. Continuous variables are displayed as mean and standard deviation, categorical variables as frequency and proportion. There are no missing values besides the ones stated in the footnote below.

a: Missing key characteristics of non-participants from Basel (n = 21).

b: Missing age at inclusion for 2 participants.

c: Missing age at diagnosis for 12 non-participants and 6 participants.

d: Missing time since diagnosis for 6 participants.

Table 2: Key characteristics of non-participants and participants in PACCS WP2, stratified by sex

	Females			Males		
	Non-participants (n = 40)[a]	Participants (n = 73)	P	Non-participants (n = 49)[a]	Participants (n = 84)	P
Age at inclusion in WP1, years[b]	12.9 ± 2.1	12.1 ± 2.4	.11	12.0 ± 2.1	12.1 ± 2.0	.94
Age at diagnosis, years[c]	4.8 ± 3.3	5.1 ± 3.2	.59	5.4 ± 3.0	5.1 ± 3.5	.68
Time since diagnosis in WP1, years[b]	7.9 ± 3.5	6.8 ± 3.2	.09	6.4 ± 2.8	6.8 ± 3.2	.37
Diagnosis (ICCC-3)			.81			.99
I. Leukemias	21 (53)	39 (53)		22 (45)	39 (46)	
II. Lymphoma	4 (10)	4 (5)		7 (14)	12 (14)	
III. CNS tumors	4 (10)	7 (10)		6 (12)	11 (13)	
IV-XII Other tumors	11 (28)	23 (32)		14 (29)	22 (26)	
Relapse	6 (15)	4 (5)	.16	9 (18)	10 (12)	.32

Note: Values are based on data extracted from medical records prior to recruitment to PACCS WP1. Continuous variables are displayed as mean and standard deviation, categorical variables as frequency and proportion. There are no missing values besides the ones stated in the footnote below.

a: Missing key characteristics of non-participants from Basel (n = 21).

b: Missing age at inclusion for 2 female participants.

c: Missing age at diagnosis for 4 female and 8 male non-participants and 5 female and 1 male participants.

d: Missing time since diagnosis for 5 female and 1 male participants.

Paper III

In review: *Journal of Adolescent and Young Adult Oncology*

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Physical Activity, Fitness, and Cardiovascular Disease Risk in Adolescent Childhood Cancer Survivors Compared to Controls. The Physical Activity in Childhood Cancer Survivors (PACCS) Study

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Running title

Physical activity, fitness, and CVD risk in cancer survivors

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Supporting Information files: 3 supplemental tables

Abstract

Purpose: Childhood cancer survivors have increased risk of cardiac late effects that can be potentially mitigated by physical activity and fitness. We aimed to 1) compare cardiovascular disease (CVD) risk between survivors and controls, and to 2) examine whether the associations of moderate-to-vigorous physical activity (MVPA), cardiorespiratory fitness (CRF), and musculoskeletal fitness (MSF) with CVD risk factors differed between survivors and controls.

Methods: Within the Physical Activity in Childhood Cancer Survivors (PACCS) study, we assessed CVD risk factors (android fat mass, systolic blood pressure, total-cholesterol/HDL-cholesterol, and HbA1c) in 157 childhood cancer survivors and 113 age- and sex-matched controls aged 9-18 years. We used multivariable mixed linear regression models to compare CVD risk factors between survivors and controls, and assess associations of MVPA, CRF, and MSF with CVD risk factors.

Results: Compared to controls, survivors had more android fat mass (861 vs. 648 g, p=0.001) and lower systolic blood pressure (114 vs. 118 mmHg, p=0.002). MVPA, CRF, and MSF were associated with lower levels of android fat mass and total-cholesterol/HDL-cholesterol, and higher systolic blood pressure in survivors. Associations of MVPA, CRF, and MSF with CVD risk factors were similar in survivors and controls ($P_{interaction}$>0.05), except the associations of CRF and MSF with android fat mass, which were stronger in survivors than in controls ($P_{interaction}$=/<0.001).

Conclusion: Due to higher levels of android fat mass and its stronger association with physical fitness in childhood cancer survivors compared to controls, survivors should get targeted interventions to increase fitness to reduce future risk of CVD.

Introduction

Currently, there are an estimated half a million childhood cancer survivors (CCS) in Europe, and the population is growing.(1) Despite good survival prognosis, CCS are at risk of treatment-related late effects, including cardiac conditions, abnormal pulmonary function, musculoskeletal deficits, and fatigue;(2,3) all conditions that can lower physical activity and fitness.

Cardiovascular disease (CVD) is highlighted as one of the most serious late effects among CCS, associated with premature mortality.(4) The literature on adult survivors of childhood cancer reports a 7-fold increased risk of dying from CVD compared to the general population.(5) Moreover, unfavourable levels of CVD risk factors are found in adult CCS compared to references.(6-10) Whether increased CVD risk is present already in adolescent CCS is not well studied.

In children and adolescents with no history of cancer, high levels of moderate-to-vigorous physical activity (MVPA) and fitness are associated with reduced CVD risk factors, such as adiposity, high blood pressure (BP), and unfavorable levels of blood lipids and glycemic control.(11-15) The few studies in young adult survivors of childhood cancer looking at PA based on self-reported data, found an association between MVPA and adiposity,(16-19) however, the majority of these studies did not find any association between MVPA and levels of BP, lipids, or glucose/insulin.(17-19). Three studies have assessed the association of physical fitness and CVD risk factors in young adult CCS.(17,19,20) As with MVPA, low CRF was found to be associated with adiposity, whereas the results were diverging for other CVD risk factors.(17,19,20) Only one study has assessed the association between MSF and CVD risk factors, in young adult CCS;(20) Schindera et al. found that low MSF was associated with adiposity, triglycerides, and metabolic syndrome.

In children and adolescents who have survived cancer, the literature shows that they have lower levels of physical activity and fitness compared to controls,(21-23) persisting many years after treatment completion, which potentially exacerbates their risk of late effects. However, the literature on the association of physical activity and physical fitness with CVD risk factors in those young CCS is scarce. The only study, looking at PA and CVD risk factors, showed an improved CVD risk profile in child and adolescent survivors with high levels of PA and stronger associations for survivors compared to controls.(18) We are not aware of any study looking at physical fitness and CVD risk factors in young CCS.

CRF and MSF are physiological characteristics dependent on both modifiable factors (i.e., MVPA) and non-modifiable factors (i.e., genetic factors).(24,25) Due to cancer treatment, survivors may reap the rewards from physical activity differently compared to the general population.(26) Knowing whether young survivors of childhood cancer already have unfavourable CVD risk factors and how they relate to physical activity and physical fitness, can help to develop targeted interventions at the right time point. In the current study, we have a unique opportunity to examine CVD risk factors in association to both MVPA, CRF, and MSF.

The aims of this study were thus to:

1) compare CVD risk factors in child and adolescent CCS with age- and sex-matched controls, and
2) examine whether the associations of device-measured MVPA, directly measured CRF, and isometric MSF with CVD risk factors differ between CCS and controls.

Methods

Study design and participants

This study is part of the international, multicenter study *Physical Activity in Childhood Cancer Survivors (PACCS).* Recruitment procedures and methodology are described in detail elsewhere.(27) Below we describe the methods relevant for this cross-sectional sub study.

We recruited CCS at their pediatric outpatient clinics when visiting for scheduled follow-up care, from three study sites (Oslo, Norway; Bergen, Norway; and Basel, Switzerland). Controls were recruited via the participating CCS (Norway), or through the hospital staff (Basel).

Inclusion criteria were age between 9-18 years, ability to perform a cardiopulmonary exercise test, and for CCS: any previous cancer disease, cancer treatment completed ≥1 year prior to recruitment, and participation in the previous part of the PACCS study. Participants were excluded if they had language or cognitive difficulties, or cardiopulmonary exercise testing was considered not possible due to physical or cognitive impairments. Participant recruitment and data collection were performed between January 2019 and January 2021.

Measures

Outcomes: CVD risk factors

We measured body composition by dual-energy X-ray absorptiometry (DXA) and estimated a*ndroid fat mass (g).* Android fat mass is shown to be more closely correlated with the unhealthy visceral adipose tissue than more traditional measures, such as body mass index and waist circumference.(28) Participants came non-fasted and in light clothing. We scanned participants from head to toe in a supine position by Lunar iDXA (GE Healthcare) using the enCORE Software Version 14 and 18 (Norway), or by Horizon A (Hologic Inc.) using the InnerCORE Software Version 13 (Basel).

After at least a 30-minute lunch break, participants entered the fitness testing lab for preparation, including resting BP measurements. We attached electrocardiogram electrodes and wires before situating an appropriate-sized BP cuff on the participant's right arm. Participants were seated in a back-supported chair with feet flat on the floor and their arms relaxed in their lap for a 5-minute rest before the BP measurements.(29) No talking was allowed during or between measurements. At least two measurements were performed using an automated oscillographic BP device (Suntech Tango+ in Oslo and in Basel (Suntech Medical Instruments); and Suntech Tango M2 in Bergen (Suntech Medical Instruments), and the lowest value of *systolic blood pressure (SBP, mmHg)* was used in the current analysis.

We collected non-fasted blood by venous sample in Norway, and by venous or capillary sample in Basel. Blood samples were collected from survivors from all three sites, and from controls in Oslo (n=49) and in Bergen (n=4). We measured lipid metabolism as the *ratio between total-cholesterol and high-density lipoprotein-cholesterol (Total/HDL)*, and glucose metabolism as *glycosylated hemoglobin (HbA1c, mmol/mol)*, which are unaffected by fasted state.(30, 31) Analyses were performed at medical laboratories by photometric methods and high-performance liquid chromatography to analyze cholesterol measures and HbA1c, respectively.

Exposures: Physical activity, cardiorespiratory fitness, and musculoskeletal fitness

Detailed information on equipment and procedures are provided in the Supplemental file 1.

We equipped participants with a hip-worn accelerometer (ActiGraph GT3X-BT) to assess MVPA (min/day) defined as ≥2000 counts per minute,(11) sampled in 10-second epochs. Participants were instructed to wear the monitor for eight consecutive days and to remove the monitor only for sleep and water-based activities. The accelerometers were initialized at a sampling rate of 30 Hertz, and accelerometer files were processed using the KineSoft analytical software version 3.3.80, restricted to hours between 06:00-23:59. Non-wear time

was defined as periods of ≥20 consecutive minutes of zero counts. Minimum eight hours/day of wear was defined as a valid day, and ≥ three valid days were required to be included in the analyses (Figure A, Supplemental file 1).

Participants performed cardiopulmonary exercise testing to assess CRF. In Norway, the test was performed by walking and running on a stationary treadmill, whereas in Basel, the test was performed on an electronically braked ergometer cycle (Supplemental file 1). Gas exchange was determined by breath-by-breath sampling, averaged over 30-second intervals, through a breathing mask. Participants performed a continuous incremental task to volitional fatigue, and $VO_{2\text{-peak}}$ was defined as the highest oxygen uptake during the test and was standardized for kg of fat-free mass ($mL \cdot fat\text{-}free\ mass^{-1} \cdot min^{-1}$). We estimated fat-free mass by subtracting fat mass from body weight derived from DXA.

After a 7-10 minutes warm-up on a treadmill/ergometer cycle, we estimated MSF by maximal isometric knee extension (kg)- and chest press (kg) where force curves were registered (Supplemental file 1). The participants performed a minimum of three attempts with 5-seconds maximal effort, with 60-second breaks, in each isometric exercise until maximum force was achieved. The criteria for a valid attempt was flattening of the force curve at the highest force achieved, without systematic fluctuations. The highest value for each exercise was registered, summarized, and standardized to body weight as a proxy of whole-body MSF.

Covariates: Age, sex, puberty stage, and cancer-related characteristics

We determined puberty stage by the self-reported Pubertal Development Stages questionnaire.(32) Participants were categorized as pre-pubertal if they reported the lowest category for all indices, post-pubertal if they reported the highest category for all indices, whereas the remaining participants were categorized as pubertal.

We extracted cancer diagnosis and a limited number of available key factors concerning cancer treatment from the CCS' medical records: age at diagnosis, cumulative anthracycline dose (Doxorubicin isotoxic equivalent dose, mg/m^2),(33) cumulative radiation dose (Gy), high-dose steroids as part of cancer treatment protocol (prednisolone equivalent dose of 60 mg/m^2/day or more; yes/no), and relapse (yes/no).

Statistical analyses

Power calculations were based on an expected 10% lower $VO_{2\text{-peak}}$ in CCS compared to controls, based on results from international studies.(34) To detect a difference of 10% in $VO_{2\text{-peak}}$ between CCS and controls (41.1 vs. 45.7 $mL \cdot kg^{-1} \cdot min^{-1}$, SD = 5.6 for both groups) with 80% power and a significance level of 5% (two-sided), we had to include 23 participants in both groups. We aimed to include 150 CCS and 150 controls to enable sub-group comparisons.

Characteristics are expressed as frequency (percentage) or mean ± SD for CCS and controls.

To compare CVD risk factors between CCS and controls (aim 1) we calculated marginal means with 95% confidence intervals (CIs) and p-values from mixed effects linear regression models, with study site and CCS/control-pair as random intercepts to account for clusters in the data, in addition to the fixed factors age, sex, and puberty stage.

To assess whether the associations of MVPA/CRF/MSF with CVD risk factors differ between CCS and controls (aim 2), we performed mixed effects linear regression models including an interaction term between the exposure (MVPA/CRF/MSF) and participant status (CCS or control). We used the delta method (by STATA's margins command) to extract marginal means and 95% CIs for CCS and controls from the mixed model. In Model 1, we adjusted only for study site and CCS-control pair as random intercepts. In Model 2, we additionally adjusted for age, sex, and puberty stage as fixed effects (Figure B, Supplemental file 1). We defined missing information on puberty stage as own category to avoid losing

participants in the analyses. We compared the fully adjusted models including either a two-way or three-way interaction term using likelihood-ratio tests; Models with a two-way interaction term yielded in general the best model fit and were thus selected for analyses.

All P-values were two-sided, and we considered P-values ≤.05 as statistically significant. Analyses and graphics were conducted using Stata statistical software (version 17.0; Stata Corporation).

Results

Study population

Of the 267 eligible invited CCS from previous parts of the PACCS project, 157 (59%) agreed to participate (Figure 1), together with 113 controls (unknown participation rate due to the recruitment procedure).

[Please insert FIGURE 1 about here]

FIGURE 1 Flowchart of the inclusion process

Demographics were similar between CCS and controls (Table 1) but survivors had higher body mass, body mass index and fat mass than controls. On average, CCS were ~5 years old at diagnosis and ~8 years from diagnosis. Half were diagnosed with leukemia; 78% had received anthracyclines; 29% radiotherapy; and 57% high-dose steroids as part of their cancer treatment protocol.

CVD risk factors

Compared to controls, CCS had more android fat mass (Table 2; marginal mean 861 vs. 648 g, P=0.001) and lower SBP (marginal mean 114 vs. 118 mmHg, P=0.002). Total/HDL and HbA1c were similar between CCS and controls.

Associations of physical activity, cardiorespiratory fitness, and musculoskeletal fitness with CVD risk factors

Figure 2 displays the associations of MVPA, CRF, and MSF with CVD risk factors, stratified by CCS and controls, with P-value for the interaction between participant status (CCS/control) and the respective exposures (MVPA/CRF/MSF). The results in Figure 2 are based on increases of 10 minutes of MVPA, 5 mL·fat-free mass^{-1}·min^{-1} of $VO_{2\text{-peak}}$ (CRF), and 0.25 total kg pushed·kg bodyweight^{-1} of MSF (Supplemental file 2; Tables A-C).

Android fat mass

There was no significant interaction between CCS and controls on the association between MVPA and android fat mass ($P_{interaction}$=.15, Figure 2A). However, higher levels of MVPA among survivors were associated with significantly less android fat mass, compared to no significant association in controls (-52 g (95% CI, -85 to -19) vs. -15 g (95% CI, -57 to 27)). The association between CRF and android fat mass was significantly different between CCS and controls ($P_{interaction}$=.001), with a significant association in CCS, but not in controls (-145 g (95% CI, -193 to -97) vs. -28 g (95% CI, -87 to 31)). MSF was associated with significantly less android fat mass in both CCS and controls (-302 g (95% CI, -361 to -243) and -143 g (95% CI, -212 to -74), respectively), however, the association was stronger in CCS than in controls ($P_{interaction}$<0.001).

Systolic blood pressure

Associations of MVPA, CRF, and MSF with SBP were similar for CCS and controls (all $P_{interactions}$>0.05). CRF was positively associated with SBP in both CCS and controls, whereas

MVPA and MSF were positively associated with SBP in CCS only. In CCS, higher MVPA, CRF, and MSF were associated with 0.7 (95% CI, 0.0 to 1.4), 1.6 (95% CI, 0.6 to 2.6), and 1.6 mmHg (95% CI, 0.2 to 2.9) higher SBP, respectively.

Blood values

There was no significant interaction between CCS and controls concerning the associations of MVPA/CRF/MSF with Total/HDL (all $P_{interactions}$>0.05). However, the associations reached statistical significance in CCS, whereas not in controls. In CCS, higher levels of MVPA, CRF, and MSF were associated with -0.1 (95% CI, -0.1 to -0.0), -0.1 (95% CI, -0.2 to -0.1), and -0.2 (95% CI, -0.3 to -0.1) lower Total/HDL, respectively. There were no associations of MVPA, CRF, or MSF with HbA1c in neither CCS nor controls.

[Please insert FIGURE 2A-D about here]

FIGURE 2 Associations of MVPA, CRF, and MSF with A. android fat mass, B. systolic blood pressure, C. Total/HDL, and D. HbA1c in CCS vs. control

Abbreviations: CCS, childhood cancer survivor; FFM, fat-free mass; MVPA, moderate-to-vigorous physical activity, MSF, musculoskeletal fitness; P, p-value for interaction; Total/HDL, total-cholesterol/high-density lipoprotein-cholesterol; VO2-peak, peak oxygen uptake.

Note: Dots represent marginal means with 95% CIs from mixed effects linear regression models with study site and CCS-control pair as random intercepts, age, sex, and puberty stage as fixed effects, and interaction term between exposure (MVPA/CRF/MSF) and participant status (CCS or control). MSF are calculated as ((maximal isometric knee extension (kg) + maximal isometric chest press (kg) / body weight (kg)). Depending on exposure variable, Model A, n=237-262; Model B, n=231-254; Model C, n=185-204; Model D, n=184-203. (For exact estimates see Supplemental file 2; Supplemental Tables A-C)

Discussion

We found that adolescent CCS had substantially more android fat mass, and lower SBP, compared to controls, whereas levels of Total/HDL and HbA1c were similar. Furthermore, the associations of MVPA, CRF, and MSF with CVD risk factors were similar in CCS and controls, except for a stronger association of CRF and MSF with android fat mass in CCS compared to controls.

In line with previous studies, we found that CCS had higher levels of adiposity (+33%) compared to healthy peers,(9,10,18,19,35) which may be considered a clinically meaningful difference.(36) Surprisingly, CCS had lower SBP than controls (- 4 mmHg). A recent study by Chow et al. found a similar lower value of SBP among a large sample of adult CCS (n = 571) compared to references.(7) However, our result contrasts with most previous studies where BP values were similar (19,35,37) or higher (8-10) in adolescent and young adult CCS vs. controls. During puberty, BP increases more rapidly compared to pre- and post-pubertal phases.(38) If cancer treatment has affected progression of puberty (i.e., slower pubertal development),(39) this might partly explain the lower SBP between our sample of adolescent CCS to controls. Our adjustment for puberty stage in the analyses was not sensitive enough to adjust for this. To our knowledge, no previous study has compared Total/HDL in CCS and controls. However, two previous studies assessing HDL-cholesterol found similar levels in young adult CCS and controls,(10,19) whereas three studies found lower levels in adolescent and young adult CCS compared to controls.(9,35,37) Few studies have compared HbA1c in CCS and controls previously. Chow et al. reported higher HbA1c in a large sample of adult CCS compared to references.(7) Levels of glucose, and hence HbA1c, are well-regulated in young people, as the pancreas can maintain its ability to secrete elevated amounts of insulin for years or decades before hyperglycemia manifests.(40) Thus, differences in our results may be explained by the different age range of our samples.

The biggest difference in CVD risk between survivors and controls was seen for android fat mass. Results from our interaction analyses may imply that CCS profit more from interventions increasing CRF and MFS to reduce android fat mass as compared to the general population. We also found stronger associations between MVPA and android fat mass in survivors compared to controls, however, without statistically significant interaction. Our findings are in accordance with two papers from Slater et al. who found a stronger association between high/low PA, high/low endurance, and CVD risk factors in adolescent (18) and adult (19) CCS compared to sibling controls. More android fat mass among CCS might explain why the associations between MVPA/CRF/MSF and CVD risk factors were generally stronger in CCS than in controls. In contrast, Slater et al. found that better endurance was associated with lower SBP in young adult CCS, and higher SBP in controls.(19) We found that higher CRF was associated with higher SBP in both CCS and controls, which might be explained by the natural increase in both CRF and SBP during puberty.(38,41) Even though we did not find any interactions between survivors and controls concerning blood values, we did find lower levels of Total/HDL in CCS who had higher levels of both MVPA, CRF, and MSF. Surprisingly, we did not observe associations between MVPA/CRF/MSF and measures of cholesterol and glucose in controls, which contrasts with previous studies.(11-14) This might be due to an underpowered control sample, especially for analyses on blood values.

The strengths of this study were the inclusion of adolescent CCS with a history of various cancer diagnoses from different study sites, and the use of objective measurement methods. The results are discussed under the assumption that the exposures are associated with the outcomes. However, a directional association cannot be inferred in this cross-sectional study. Thus, it is unclear whether higher MVPA/CRF/MSF is associated with for example a lower level of adiposity, or whether a higher level of adiposity is associated with lower MVPA/CRF/MSF. Another limitation was the few blood samples from controls, which might explain the contrasting finding of no or few associations between MVPA/CRF/MSF and

CVD risk factor in controls.(11-15) Further, equipment or measurement methods were different between study sites. However, we accounted for this in the analyses by adjusting for study site as random intercept. Similarly, we adjusted for CCS-control pair as a random intercept to account for similarities between CCS and controls that were friends/family. Self-reporting of puberty stage might be prone to bias, however, a recent study found substantial agreement between Pubertal Development Stages and Tanner scale when each scale was combined into three categories.(42) The relatively low participation rate (59%) might result in a selected sample towards participants with interest in physical activity and fitness, impacting the generalizability of our results. Our comparison of participants and non-participants in a previous publication from the current project found no significant differences in key characteristics (sex, age, age at diagnosis, time since diagnosis, diagnosis, relapse).(26) However, this is mainly relevant for aim 1 and not the investigations concerning factors associated with CVD risk since the participants still covered a broad range in the outcome and exposure variables.

Conclusions

Our results showed that adolescent CCS had more android fat mass compared to their peers. Furthermore, our findings indicate that CCS may benefit more from increasing their CRF and MSF compared to controls, possibly due to a greater potential for reducing android fat mass. Finally, we found that also MSF is significantly associated with CVD risk factors; which has not been shown in this population previously.

Yet, further research using longitudinal designs is needed to assess the direct effect of increasing PA and fitness on android fat mass and other CVD risk factors in CCS.

Due to higher levels of android fat mass already seen in young survivors of childhood cancer and its stronger association with physical fitness compared to controls, this population should get targeted interventions to increase fitness to reduce future risk of CVD.

Ethical approval and consent to participate

The PACCS study was approved by the Norwegian Regional Committee for Medical Ethics (reference number 2018/739), the Data protection Officer at Oslo University Hospital, and the Ethics Committee of North-Western and Central Switzerland (project ID 2019-00410). Written informed consent was collected from all participants/parents.

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Author contributions

Mari Bratteteig: Formal analysis, investigation, methodology, visualization, writing – original draft, writing – review & editing. **Corina Silvia Rueegg:** Methodology, supervision, validation, visualization, writing – review & editing. **Truls Raastad:** Conceptualization, funding acquisition, project administration, writing – review & editing. **May Grydeland:** Conceptualization, funding acquisition, investigation, methodology, project administration, supervision, writing – review & editing. **Ingrid Kristin Torsvik:** Investigation, writing – review & editing. **Christina Schindera:** Investigation, writing – review & editing. **Ellen Ruud:** Conceptualization, funding acquisition, project administration, supervision, writing – review & editing. **Sigmund Alfred Anderssen:** Conceptualization, funding acquisition,

methodology, project administration, supervision, visualization, writing – review & editing.

All authors have approved the final version of the manuscript, and all have agreed to be accountable for all aspects of the work.

Conflict of Interest Statement

The authors have no conflict of interest, financial or otherwise, to disclose.

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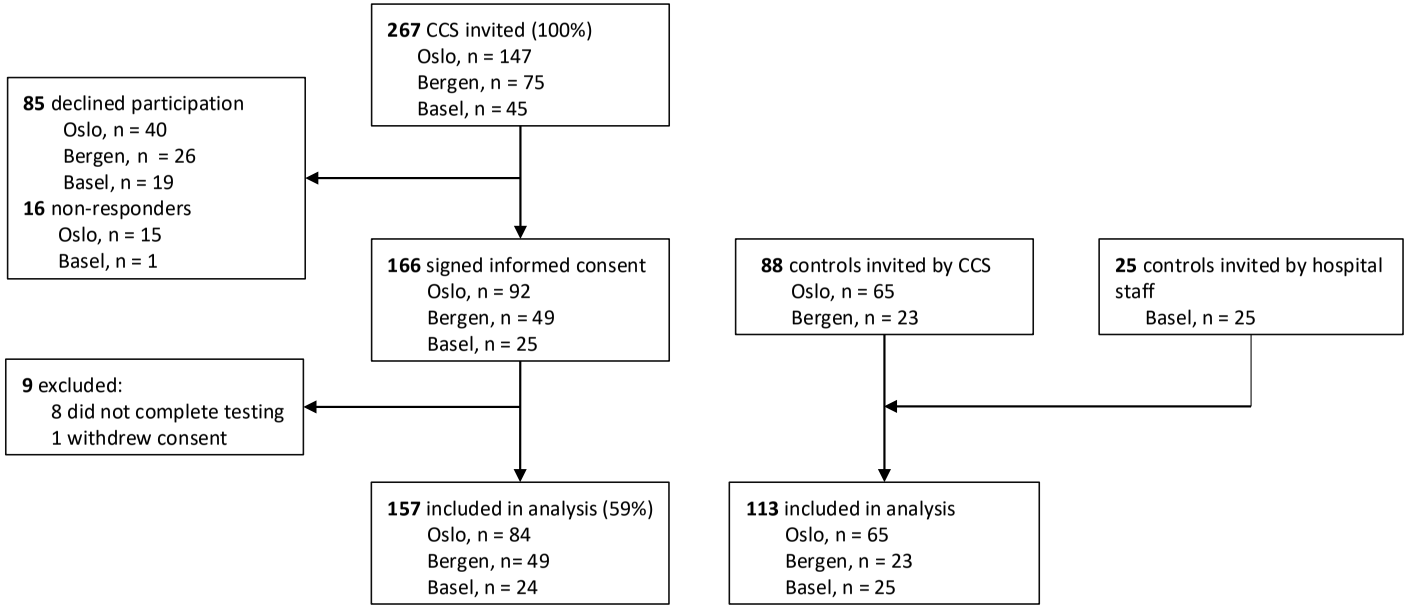


FIGURE 1 Flowchart of the inclusion process

TABLE 1: Characteristics of childhood cancer survivors and controls

	CCS (n = 157, 47% girls)	**Controls (n = 113, 50% girls)**
Age at study, years	13.4 ± 2.5	13.2 ± 2.6
Puberty stage[a], frequency (%) Pre-pubertal Pubertal Post-pubertal	 36 (23) 112 (71) 9 (6)	 28 (26) 74 (69) 6 (6)
Caucasian ethnicity, frequency (%)	146 (93)	109 (96)
Height (cm)	158 ± 14	158 ± 15
Body mass (kg)	50.3 ± 14.9	47.8 ± 13.7
Body mass index (kg/m^2)	19.9 ± 3.7	18.8 ± 2.6
Fat mass (kg)[b]	15.0 ± 7.6	12.4 ± 5.1
Fat-free mass (kg)[b]	35.6 ± 10.0	35.3 ± 11.0
Age at diagnosis, years	5.2 ± 3.4	NA
Time since diagnosis, years	8.2 ± 3.6	NA
Diagnoses (ICCC-3), frequency (%) I. Leukaemia II. Lymphoma III. CNS tumor IV-XII Other cancer[c]	 78 (50) 16 (10) 18 (11) 45 (29)	NA
Anthracyclines[d], frequency (%) Cumulative dose (mg/m^2), mean (range)	121 (78) 161 (45-450)	NA
Any radiotherapy, frequency (%) Cumulative dose (Gy), mean (range)[e]	45 (29) 33 (12-70)	NA
High-dose steroid treatment[f], frequency (%)	90 (57)	NA
Relapse, frequency (%)	13 (8)	NA

Numbers are means with SDs if not stated otherwise. Abbreviations: CCS, childhood cancer survivors; CNS, central nervous system; Gy, gray; ICCC-3, international classification of childhood cancer – third edition; NA, not applicable.

a: Missing value on puberty stage in five controls.

b: Missing value on fat mass and fat-free mass in three CCS and one control.

c: Includes neuroblastoma (n=9), eye cancer (n=2), kidney cancer (n=14), liver cancer(n=2), bone tumor (n=6), soft-tissue sarcoma (n=10), others (n=2).

d: Missing info on anthracyclines in two CCS and anthracycline dose in nine CCS.

e: Missing radiotherapy dose in one CCS.

f: As part of cancer treatment protocol (prednisolone equivalent dose of 60 mg/m2/day or more).

TABLE 2: Marginal means of CVD risk factors with 95% CIs in CCS vs. controls

CVD risk factors	CCS (n = 157)	Controls (n = 113)	
	Mean (95% CI)	Mean (95% CI)	P-value
Android fat mass (g)[a]	861 (770-952)	648 (542-754)	0.001
Systolic BP (mmHg)[b]	114 (106-121)	118 (111-126)	0.002
Total/HD[c]	3.1 (2.9-3.2)	2.9 (2.7-3.1)	0.23
HbA1c (mmol/mol)[d]	33 (32-35)	34 (32-36)	0.19

Abbreviations: BP, blood pressure; CCS, childhood cancer survivors; CVD, cardiovascular disease; HbA1c, glycosylated hemoglobin; Total/HDL, total-cholesterol/high-density lipoprotein-cholesterol.

Marginal means with 95% CIs and p-values from mixed effects linear model with study site and CCS/control-pair as random intercepts and age, sex, and puberty stage as fixed effects.

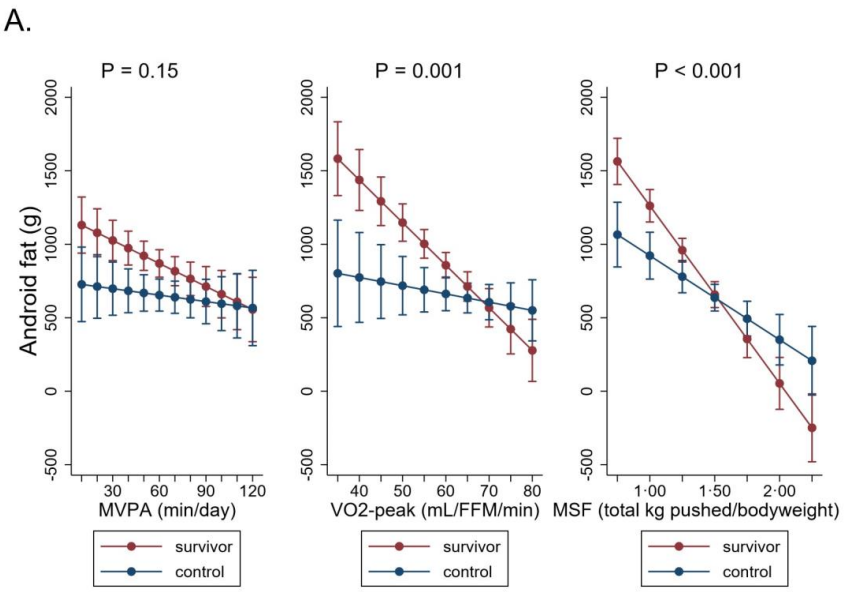
a: Missing value for android fat mass in three CCS and one control.

b: Missing value for Systolic BP in seven CCS and four controls.

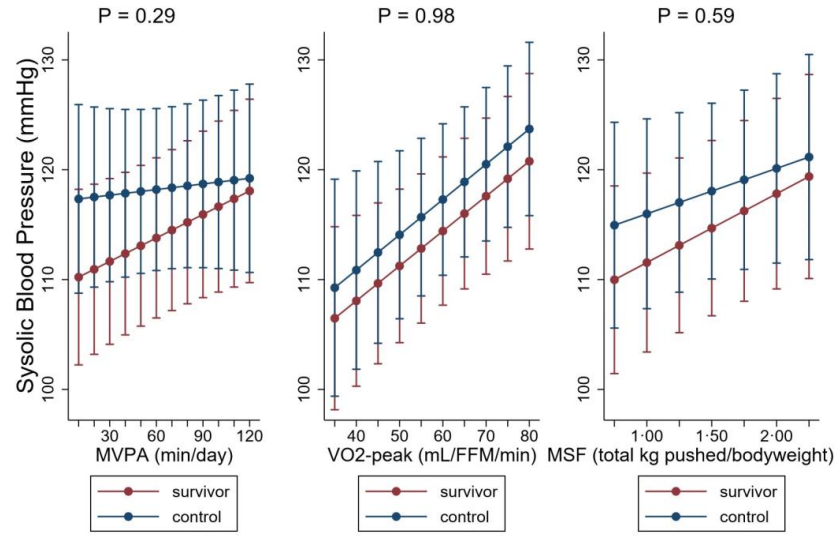
c: Missing value for Total/HDL in seven CCS and 55 controls.

d: Missing values for HbA1c in seven CCS and 56 controls.

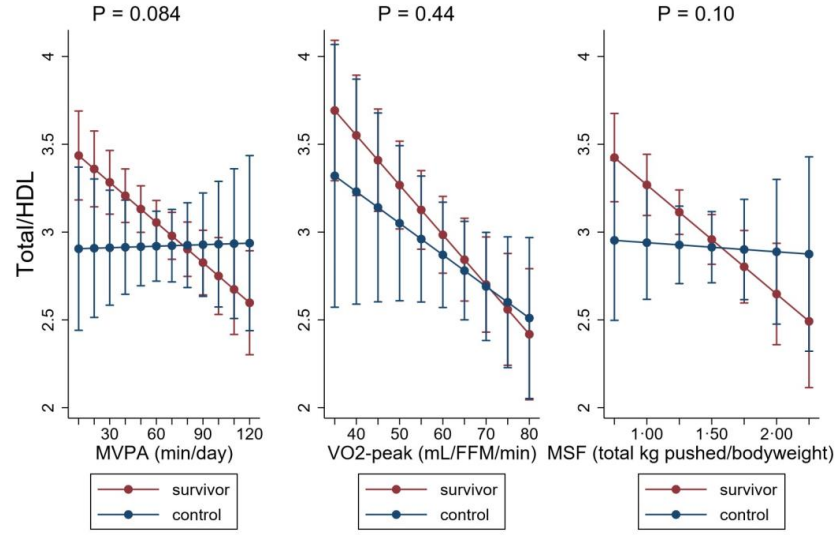
Note: Blood samples were drawn from controls mainly from Oslo, hence the large number of missing Total/HDL and HbA1c values in this group.



B.


P = 0.29
P = 0.98
P = 0.59
Sysolic Blood Pressure (mmHg)
100
110
120
130
30 60 90 120
MVPA (min/day)
40 50 60 70 80
VO2-peak (mL/FFM/min)
1·00 1·50 2·00
MSF (total kg pushed/bodyweight)
survivor
control

C.


P = 0.084
P = 0.44
P = 0.10
Total/HDL
2
2.5
3
3.5
4
30 60 90 120
MVPA (min/day)
40 50 60 70 80
VO2-peak (mL/FFM/min)
1·00 1·50 2·00
MSF (total kg pushed/bodyweight)
survivor
control

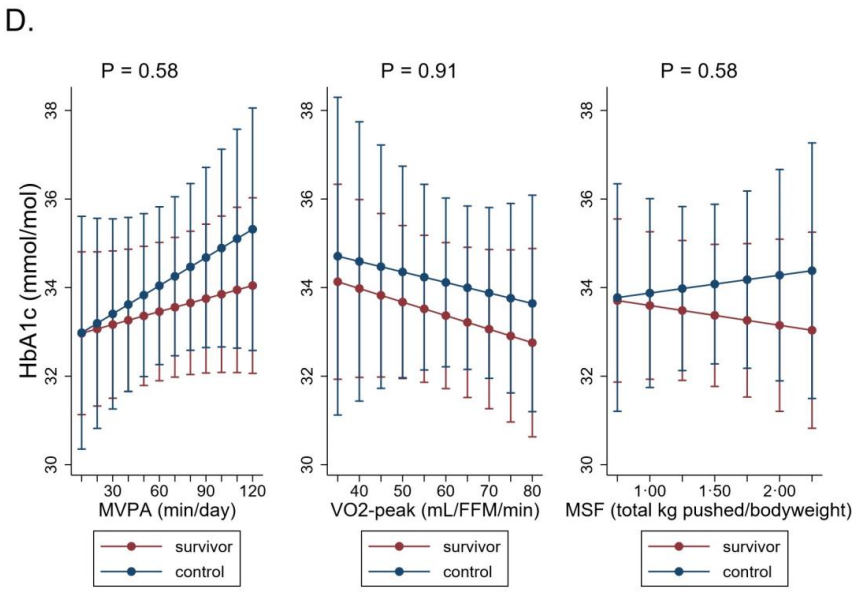


FIGURE 2 Associations of MVPA, CRF, and MSF with A. android fat mass, B. systolic blood pressure, C. Total/HDL, and D. HbA1c in CCS vs. control

Abbreviations: CCS, childhood cancer survivor; FFM, fat-free mass; MVPA, moderate-to-vigorous physical activity, MSF, musculoskeletal fitness; P, p-value for interaction; Total/HDL, total-cholesterol/high-density lipoprotein-cholesterol; VO2-peak, peak oxygen uptake.

Note: Dots represent marginal means with 95% CIs from mixed effects linear regression models with study site and CCS-control pair as random intercepts, age, sex, and puberty stage as fixed effects, and interaction term between exposure (MVPA/CRF/MSF) and participant status (CCS or control). MSF are calculated as ((maximal isometric knee extension (kg) + maximal isometric chest press (kg) / body weight (kg)). Depending on exposure variable, Model A, n=237-262; Model B, n=231-254; Model C, n=185-204; Model D, n=184-203. (For exact estimates see Supplemental file 2; Supplemental Tables A-C)

Supplemental file 1 (Methods)

Physical activity

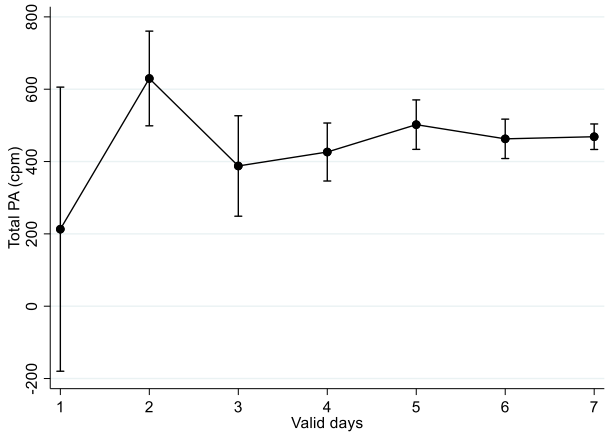


Figure A Margins plot showing participant's total physical activity (mean counts per minute/day with 95% CI) according to their respective number of valid days (n = 251).

Cardiorespiratory fitness

The cardiopulmonary exercise testing equipment was volume- and gas calibrated daily to ensure valid measurements, and the tests were performed by qualified test personnel according to standardised procedures.

In Oslo and Bergen, the cardiopulmonary exercise testing was performed by walking and running on a stationary treadmill (Rodby RL2700E, in Oslo; and Woodway PPS 55 Med, Woodway GmbH, in Bergen). The breathing mask (Hans Rudolph Inc, 2700 series) was connected to a metabolic analyser (Jaeger Oxycon Pro, Viasys Healthcare GmbH, in Oslo; and Jaeger Vyntus CPX, Vyaire Medical GmbH, in Bergen). A modified Balke protocol for children was applied.[1] Initial workload after habituation to the treadmill was 3 km/h, 4 km/h, and additionally 4% inclination, respectively, for the first three minutes. Thereafter, workload was increased every minute by increasing speed by 1 km/h and inclination by 2% every other minute, respectively. The test was stopped and considered maximal when the participant refused further increase in workload or until subjective exhaustion.

In Basel, an incremental cycling task was performed using an electronically braked ergometer (Ergoline 800) and a Quark B2 metabolic cart (Cortex MetaLizer 3B). Work rate was increased every minute by 15–20 W, depending on participant's height and physical fitness until the minimal cadence of 60 revolutions per minute could not be maintained or subjective exhaustion.[2]

Criteria for aborting the cardiopulmonary exercise testing were decreasing systolic blood pressure or multiple ventricular extrasystoles during the test. There was always an extra person helping during cardiopulmonary exercise testing, both for safety reasons and for intense cheering to ensure maximal effort.

Musculoskeletal fitness

The maximal isometric exercises were performed on an ergometer bench specifically designed for children (GYM2000). A strain gauge (US2A 100 kg) was attached to the ergometer to measure force in kg, together with a custom-made amplifier. The force was registered at a frequency of 100 Hz in the belonging software (MVC recorder and Siri version 2). The ergometer was controlled before each test day.

During knee extension, participants sat at the end of the bench so that the backside of the legs touched the edge of the bench (Image A). The exercise was performed on the dominant leg. Participants were instructed to perform the exercise with a straight back, grabbing the bench on either side, and to extend their knee maximally, straight forward and continuously for 5 seconds.

During chest press, participants were situated on their back in a supine position on the ergometer bench, with their knees flexed and their feet stably placed on the bench (Image B). Participants' grip on the barbell was adjusted so that the elbow angle was 90°, and elbow joints were controlled to be in approximate height with the shoulder joint. The participants were instructed to push maximally straight up, continuously for 5 seconds.

Image A Positioning and execution of maximal isometric knee extension *(Photographer: Idunn Lyng Brekken)*.

Image B Positioning and execution of maximal isometric chest press (the elbow angle is a bit too wide on the image to the right) *(Photographer: Idunn Lyng Brekken)*.

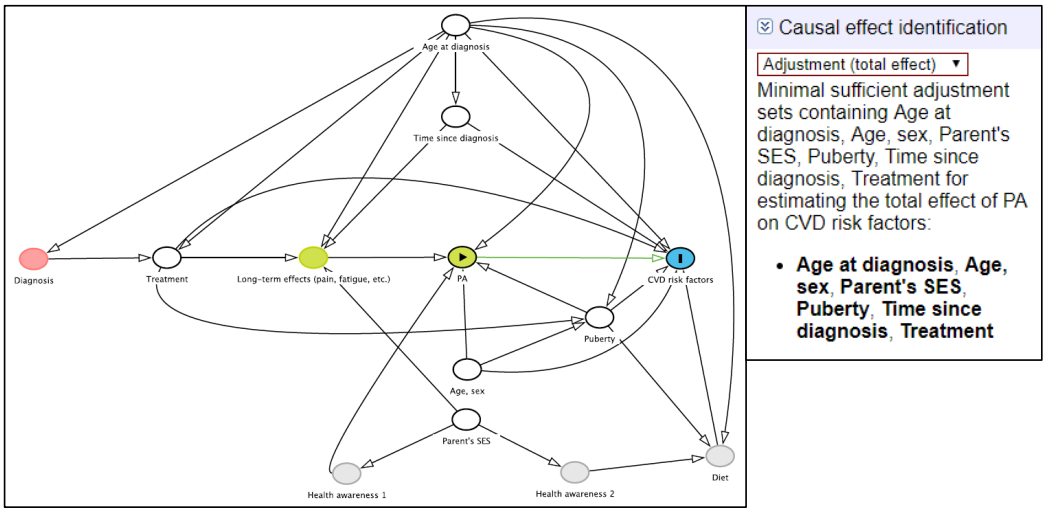


Figure B Directed acyclic graph used for model specification

Abbreviations: CVD, cardiovascular disease; PA, physical activity; SES, socio-economic status.

Note: We did only have information on parent's SES (parental education) in the childhood cancer survivors. Thus, we did not adjust for parent's SES in our mixed effects linear regression model.

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Supplemental file 2 (Results)

TABLE A Associations between moderate-to-vigorous physical activity (10-min increase) and CVD risk factors

	Model 1, β-coefficients, (95% CI)				Model 2, β-coefficients, (95% CI)				Interaction from model 2 MVPA x CCS/control
	CCS (n = 135)	P-value	Controls (n = 102)	P-value	CCS (n = 135)	P-value	Controls (n = 102)	P-value	$P_{interaction}$
Android fat mass (g)	-63 (-96 to -30)	<0.001	-27 (-69 to 1)	0.20	-52 (-85 to -19)	0.002	-15 (-57 to 27)	0.50	0.15
Systolic BP (mmHg)[a]	0.4 (-0.3 to 1.1)	0.29	-0.2 (-1.1 to 0.6)	0.56	0.7 (0.0 to 1.4)	0.036	0.2 (-0.6 to 1.0)	0.68	0.29
Total/HDL[b]	-0.1 (-0.1 to -0.0)	<0.001	0.0 (-0.1 to 0.1)	0.91	-0.1 (-0.1 to -0.0)	0.001	0.0 (-0.1 to 0.1)	0.94	0.084
HbA1c (mmol/mol)[c]	0.1 (-0.1 to 0.3)	0.31	0.2 (-0.1 to 0.6)	0.22	0.1 (-0.1 to 0.3)	0.34	0.2 (-0.2 to 0.6)	0.25	0.58

Abbreviations: BP, blood pressure; CCS, childhood cancer survivors; HbA1c, glycosylated haemoglobin; MVPA, moderate- to vigorous physical activity; Total/HDL, total-cholesterol/high-density lipoprotein cholesterol.

Model 1: Includes interaction term between exposure and type of participant. Adjusted for site and CCS-control pair.

Model 2: Includes interaction term between exposure and type of participant. Adjusted for site, CCS-control pair, age, sex, and puberty stage.

a: Missing value for SBP in 4 CCS and 2 controls.

b: Missing value for Total/HDL in 3 CCS and 49 controls.

c: Missing value for HbA1c in 3 CCS and 50 controls.

Note: Blood samples were drawn from controls mainly from Oslo, hence the large number of missing Total/HDL and HbA1c values in this group.

TABLE B Associations between cardiorespiratory fitness (5 mL·fat-free mass^{-1}·min^{-1} increase in $VO_{2\text{-peak}}$) and CVD risk factors

	Model 1, β-coefficients, (95% CI)				Model 2, β-coefficients, (95% CI)				Interaction from model 2 $VO_{2\text{-peak}}$ x CCS/control
	CCS (n = 152)	P-value	Controls (n = 110)	P-value	CCS (n = 152)	P-value	Controls (n = 110)	P-value	$P_{interaction}$
Android fat mass (g)	-151 (-200 to -101)	<0.001	-49 (-109 to 10)	0.11	-145 (-193 to -97)	<0.001	-28 (-87 to 31)	0.35	0.001
Systolic BP (mmHg)[a]	1.5 (0.4 to 2.3)	0.007	1.2 (-0.2 to 2.4)	0.074	1.6 (0.6 to 2.6)	0.002	1.6 (0.4 to 2.9)	0.011	0.98
Total/HDL[b]	-0.1 (-0.2 to -0.1)	<0.001	-0.1 (-0.2 to 0.0)	0.14	-0.1 (-0.2 to -0.1)	<0.001	-0.1 (-0.2 to 0.0)	0.13	0.44
HbA1c (mmol/mol)[c]	-0.1 (-0.4 to 0.2)	0.41	-0.0 (-0.6 to 0.5)	0.87	-0.2 (-0.5 to 0.2)	0.34	-0.1 (-0.6 to 0.4)	0.66	0.91

Abbreviations: BP, blood pressure; CCS, childhood cancer survivors; HbA1c, glycosylated haemoglobin; Total/HDL, total-cholesterol/high-density lipoprotein cholesterol; VO2-peak, maximal oxygen consumption.

Model 1: Includes interaction term between exposure and type of participant. Adjusted for site and survivor-control pair.

Model 2: Includes interaction term between exposure and type of participant. Adjusted for site, CCS-control pair, age, sex, and puberty stage.

b: Missing value for SBP in 5 CCS and 3 controls.

c: Missing value for Total/HDL in 6 CCS and 52 controls.

d: Missing value for HbA1c in 6 CCS and 53 controls.

Note: Blood samples were drawn from controls mainly from Oslo, hence the large number of missing Total/HDL and HbA1c values in this group.

TABLE C Associations between musculoskeletal fitness (0.25 kg/body weight increase) and CVD risk factors

	Model 1, β-coefficients, (95% CI)				Model 2, β-coefficients, (95% CI)				Interaction from model 2 MSF x CCS/Control
	CCS (n = 147)	P-value	Controls (n = 109)	P-value	CCS (n = 147)	P-value	Controls (n = 109)	P-value	$P_{interaction}$
Android fat mass (g)	-248 (-308 to -189)	<0.001	-123 (-193 to -52)	0.001	-302 (-361 to -243)	<0.001	-143 (-212 to -74)	<0.001	<0.001
Systolic BP (mmHg)[a]	2.2 (0.9 to 3.5)	0.001	1.5 (-0.1 to 3.1)	0.069	1.6 (0.2 to 2.9)	0.021	1.0 (-0.6 to 2.7)	0.21	0.59
Total/HDL[b]	-0.1 (-0.2 to -0.0)	0.017	0.3 (-0.1 to 0.2	0.71	-0.2 (-0.3 to -0.1)	0.002	-0.0 (-0.2 to 0.1)	0.87	0.10
HbA1c (mmol/mol)[c]	-0.1 (-0.4 to 0.3)	0.80	0.1 (-0.5 to 0.8)	0.68	-0.1 (-0.5 to 0.8)	0.60	0.1 (-0.6 to 0.8)	0.77	0.58

Abbreviations: BP, blood pressure; CCS, childhood cancer survivors; HbA1c, glycosylated haemoglobin; MSF, musculoskeletal fitness; Total/HDL, total-cholesterol/high-density lipoprotein cholesterol.

Model 1: Includes interaction term between exposure and type of participant. Adjusted for site and survivor-control pair.

Model 2: Includes interaction term between exposure and type of participant. Adjusted for site, CCS-control pair, age, sex, and puberty stage.

a: Missing SBP in 2 CCS and 2 controls.

b: Missing Total/HDL in 4 CCS and 52 controls.

c: Missing HbA1c in 4 CCS and 53 controls.

Note: Blood samples were drawn from controls mainly from Oslo, hence the large number of missing Total/HDL and HbA1c values in this group.

Appendices

- WP1: Application to the Regional Ethics Committee (Initial name: Fysisk aktivitet hos barn og ungdommer etter kreftbehandling, “FysAk-Barnekreft”)
- WP1: Approval from the Regional Ethics Committee to carry out “FysAk-Barnekreft” (national study)
- WP1: Approval to expand the project to become an international, multicenter study (new name: Physical Activity in Childhood Cancer Survivors, “PACCS”)
- WP2: Approval from the Regional Ethics Committee

- WP1 information letter to children/adolescents under 16 years, and their guardians
- WP1 information letter to adolescents 16 years
- WP2 information letter to children under 12 years
- WP2 information letter to adolescents 12-18 years
- WP2 information letter to guardians
- WP2 information letter to children under 12 years in the control group
- WP2 information letter to adolescents 12-18 years in the control group
- WP2 information letter to guardians in the control group

Prosjektsøknad Skjema for søknad om godkjenning av forskningsprosjekt i de regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK)

Dokument-id: 721846

Fysisk aktivitet hos barn og ungdommer etter kreftbehandling, "FysAk-Barnekreft"

1. Generelle opplysninger

1.1 Prosjektleder

Navn:	Ellen Ruud
Akademisk grad:	Dr.med
Klinisk kompetanse:	Overlege i barneonkologi
Stilling:	Overlege
Hovedarbeidssted:	OUS
Arbeidsadresse:	Kvinne- og barneklinikken
Postnummer:	0424
Sted:	Oslo
Telefon:	23074560
Mobiltelefon:	41510330
E-post adresse:	elruud@ous-hf.no

1.2 Prosjekttittel

Norsk tittel	Fysisk aktivitet hos barn og ungdommer etter kreftbehandling, "FysAk-Barnekreft"
Vitenskapelig tittel	Level of physical activity in childhood cancer survivors

1.3 Forskningsansvarlig

Institusjon	Kontaktperson	Stilling	E-post adresse
1. Oslo Universitetssykehus	Peder H Utne	Head of Research	grants@ous-hf.no

	Administration & Biobank

1.4 Initiativtaker

Hvem er initiativtaker til prosjektet?	Prosjektleder og/eller forskningsansvarlig institusjon (bidragsforskning)

1.5 Utdanningsprosjekt

Er prosjektet del av en utdanning eller doktorgrad?	Ja
Studium/fag	Medisin
Nivå	PhD

1.6 Prosjektmedarbeidere

Navn	Stilling	Institusjon	Akademisk rolle	Prosjektrolle
1. Lene Thorsen	forsker	OUS	PhD	WP-leder
2. May Grydeland	Førsteamenuensis	Norges idrettshøyskole	PhD	WP-leder
3. Hanne C Lie	forsker	OUS	PhD	Prosjektmedarbeider
4. Sigmund A Anderssen	professor	Norges Idrettshøyskole	PhD	Co-prosjektleder
5. Trine Stensrud	Førsteamenuensis	Norges Idrettshøyskole	PhD	Prosjektmedarbeider
6. Truls Raastad	professor	Norges Idrettshøyskole	PhD	Prosjektmedarbeider
7. Iren Matthews	overlege	OUS	PhD	Prosjektmedarbeider
8. Elna H Larsen	Sykepleier/koordinator	OUS	master i sykepleie	Studiesykepleier og koordinator
9. Karin Hammeren	Studiesykepleier	OUS	sykepleier	Sykepleier/koordinator

1.7 Tidsramme for prosjektet

Prosjektstart dato	01.09.2016
Prosjektslutt dato	31.12.2020

1.8 Offentlig innsyn

Søkes det om unntak fra offentlig innsyn i søknad eller vedlegg?	Nei

1.9 Samarbeid med utlandet

Har prosjektet noen form for samarbeid med utlandet?	Nei

1.10 Annet prosjekt med betydning for vurderingen

Er det noe annet prosjekt som kan ha betydning for vurderingen av det aktuelle prosjektet?	Nei

2. Prosjektopplysninger

2.1 Oppsummering av forskningsprosjektet

Prosjektbeskrivelse

Barn og ungdommer som har gjennomgått kreftbehandling opplever ofte utfordringer med hverdagslige aktiviteter, som lek og deltagelse i idrettslag og kroppsøvingstimene. Vi vet ikke eksakt omfanget av problemet, om noen undergrupper har større problemer enn andre, mulige barrierer og behovet for oppfølging. Mer kunnskap vil bidra til å lage målrettede tiltak til disse barna og ungdommene. Vi ønsker derfor å invitere 250 barn og ungdommer mellom 9 og 15 år, som møter til poliklinisk kontroll på Seksjon for Kreftsykdommer hos Barn ved Rikshospitalet, minst12 måneder etter avsluttet behandling, til en tverrsnittstudie. Gjennom intervju, spørreskjema og aktivitetsmålere har studien til hensikt å undersøke selvrapportert og objektivt målt fysisk aktivitetsnivå sammenlignet med aktivitetsnivået blant barn og ungdommer generelt, deltagelse i kroppsøvingstimene på skolen, barrierer som gjør det vanskelig å være fysisk aktiv, behov for oppfølging, energinivå og hvordan de har det generelt.

2.2 Legemiddelutprøving

Legemiddelutprøving Nei

2.3 Forskningsdata

2.3.1 Tidligere registrerte opplysninger Ja

Spesifiser hvilke typer opplysninger

Pasientjournaldata fra pasientens journal ved OUS om kreftdiagnose, behandling, oppfølging og komplikasjoner.

☒ Pasientjournal eller annet behandlingsrettet register

☒ Pasientjournal

Oppgi hvilke pasientjournaler

Pasientjournaldata fra pasientens somatiske journal ved OUS

Hvilke opplysninger hentes fra pasientjournal?

Data om kreftdiagnose, behandling, oppfølging og komplikasjoner.

2.3.2 Nye helseopplysninger Ja

Spesifiser hvilke typer helseopplysninger

Spørreskjemaundersøkelse på livsstil, fysisk aktivitet, livskvalitet, mestring og kronisk trøtthet.

2.3.3 Humant biologisk materiale Nei

2.4 Studiepopulasjon

2.4.1 Antall forskningsdeltakere og styrkeberegning

Vi planlegger å inkludere 250 deltakere. Antallet er valgt for å kunne bevise en forskjell i fysisk aktivitet på 10 % med teststyrke 80 % i forhold til et nasjonalt representativt referansemateriale bestående av ca 5000 friske barn og ungdom etablert på Norges idrettshøyskole.

2.4.2 Beskrivelse av forskningsdeltakere/utvalg

☒ Pasienter/klienter

Spesifiser hvilke pasienter

Barn/ungdommer i aldersgruppen 9-15 år som har gjennomført og avsluttet kreftbehandling minst ett år før inklusjon i denne aktuelle studien.

Begrunn valg av pasientgruppe

Ungdommer som har blitt behandlet for kreft har livslang høy risko for til dels livstruende seneffekter, og internasjonale rapporterer tyder på at gruppen har et for lavt fysisk aktivitetsnivå allerede i ungdomsperioden. Vi ønsker å studere aktivitetsnivået hos norske ungdommer etter kreft for evt å planlegge en senere intervensjonsstudie. Ungdomstiden er en viktig periode for positiv livsstilpåvirkning.

☒ Mindreårige

☒ Under 12 år

☒ 12-16 år

2.5 Forskningsmetode

2.5.1 Metode for analysering av data

☒ Statistiske (kvantitative) analysemetoder

☑ Fortolkende (kvalitative) analysemetoder

2.5.2 Metode for innhenting av data

☒ Spørreskjema

☒ Intervju

Lydopptak Ja

2.6 Begrunnelse for valg av data og metode

Redegjør for den faglige og vitenskapelige begrunnelsen for valg av data og metode

Kombinasjonen av spørreskjemaundersøkelser for egenrapportert fysisk aktivitet og objektivt målt aktivitetsnivå med aktivitetsmåler tror vi gir et godt bilde av reelt av aktivitetsnivået hos ungdommene og evt barrierer mot fysisk aktivitet. I tillegg vil man gjøre et kvalitativt intervju av de 20 - 30 første representative deltakerne inntil man har oppnådd metning for nye temaer rundt aktivitetsbarrierer og fascilitatorer. Disse intervjuene vil først og fremst være viktig for planlegging av intervensjoner i evt senere studier.

3. Informasjon, samtykke og personvern

3.1 Samtykke vil bli innhentet

Samtykke vil bli innhentet	Ja

For hvilke deltakere, opplysninger og evt. prøver vil samtykke bli innhentet?

Samtykke barn/ungdommer i alderen 9-15 år som tidligere har gjennomført kreftbehandling for spørreskjemaundersøkelse, aktivitetsregistrering og intervju. Foreldrene gir samtykke på barnas vegne, etter å ha ha rådført seg med sine barn, siden disse barna/ungdommene ikke er samtykkekompetente

Hvordan vil deltakerne bli identifisert, kontaktet og rekruttert? Beskriv rekrutteringsprosedyre og begrunn evt. avvik fra skriftelig samtykke

De blir identifisert i forbindelse med en planlagt poliklinisk konsultasjon på Seksjon for Pediatrisk Blod og Kreftsykdommer, OUS-Rikshospitalet. I forbindelse med innkalling til denne konsultasjonen, vil de motta informasjon om studien. En studiesykepleier vil i tillegg ringe de opp i forkant av konsultasjonen for å forsikre seg om at de har mottatt informasjonsbrevet og evt besvare spørsmål.

Beskriv inklusjonskriterier

Alder 9 - 15 år, minst ett år siden avsluttet kreftbehandling, følges opp på Seksjon for Pediatrisk Blod og Kreftsykdommer, OUS.

Beskriv eksklusjonskriterier

Tidligere behandlet for hjernesvulst, manglende norskkunnskaper, manglende samtykke.

3.2 Samtykke er allerede innhentet

Samtykke er allerede innhentet	Nei

3.3 Det søkes om fritak fra kravet om å innhente samtykke

Det søkes om fritak fra kravet om å innhente samtykke	Nei

4. Avveining av nytte og risiko ved prosjektet

4.1 Fordeler

Angi fysisk, psykisk, sosial og/eller praktisk fordel/nytte/gagn nå eller i fremtida for den enkelte pasient/deltaker, grupper av personer, samfunnet og/eller vitenskapen .

Økt fokus på sunn livsstil er et gode for alle ungdommer og ikke minst de som har vært gjennom intensiv kreftbehandling. Barnekreftoverlevere har betydelig økt risiko for seneffekter, og risikoen øker med tiden. Vi tror at økt fysisk aktivitetsnivå er positivt og kan i noen tilfeller bremse opp utviklingen av seneffekter. Bare det faktum at vi

registrerer aktivitetsnivået kan få den enkelte til å endre livsstil i en sunnere retning, selv om de ikke får tilbakemelding på resultater fra egen innsats.

4.2 Ulemper

Angi fysisk, psykisk, sosial og/eller praktisk risiko/skade/ubehag/belastning/uleilighet nå eller i fremtida for den enkelte pasient/deltaker, grupper av personer, samfunn og/eller miljø .

Vi kan ikke se at det er store ulemper ved å delta i studien, foruten den lille praktiske utfordringen det er å ha på seg et belte med aktivitetsmåler i en uke.

4.3 Tiltak

Redegjør for eventuelle særlige tiltak for å ivareta og beskytte pasientene/deltakerne i forskningsprosjektet og for å begrense mulig risiko/ulempe

Det vil bli koplet en studiesykepleier til prosjektet som blir lett tilgjengelig på mobiltelefon i tilfelle spørsmål og oppklaringsbehov fra deltakerne. Ellers er det lite risiko/ulempe forbundet med dette kartleggingsprosjektet.

4.4 Forsvarlighet

Hvorfor er det forsvarlig å gjennomføre prosjektet? Gi en begrunnet avveining av fordelene og ulempene ved forskningsprosjektet.

Prosjektet vil frembringe nyttig basisinformasjon om barnekreftoverlevere i aldersgruppen 9 - 15 års livsstil og fysiske aktivitetsnivå. Et viktig grunnlag for senere intervensjonsforskning på livsstil hos barnekreftoverlevere i ungdomsalderen. Man ser få ulemper med prosjektet.

5. Sikkerhet, interesser og publisering

5.1 Personidentifiserbare opplysninger

I hvilken form skal personidentifiserbare opplysninger og prøver brukes i prosjektet?

☒ Avidentifisert med koblingsnøkkel

Gi informasjon om hvordan koblingsnøkkelen oppbevares og hvem som har tilgang til denne

Koblingslisten med pasient identifikasjon og korresponderende studienr vil oppbevares i papirform på låst kontor.

5.2 Internkontroll og sikkerhet

5.2.1 Hvordan skal personidentifiserbare opplysninger og prøver oppbevares?

☒ Innelåst oppbevaring

Redegjør nærmere for oppbevaringsmåte, låse- og adgangsrutiner mv

Koblingsnøkkelen på låst kontor. Studiedata tilknyttet pasientens studienr på forskningsserver på institusjonen.

☒ Videoopptak/fotografi/lydopptak

Ikke på PC

☒ Manuelt/papir

☒ Koblingsnøkkel og data oppbevares atskilt fra hverandre

5.3 Forsikring for forskningsdeltakere

☒ Pasientskadeloven

5.4 Vurdering av andre instanser

Prosjektet har blitt vurdert/skal vurderes av:

☒ Egen institusjon

☒ Internt personvernombud

5.5 Interesser

Finansieringskilder

Det søkes om forskningsmidler fra ulike steder, blant annet Norges Forskningsråd. Foreløpig er ikke finansiering av PhD avklart, men vi har driftsmidler fra Helse SØ for å gjennomføre selve studien.

Godtgjøring til institusjon

Ingen godtgjøring er aktuell

Honorar prosjektleder/-medarbeidere

Ingen spesiell honorering av prosjektgruppen.

Kompensasjon for forskningsdeltakere

Ingen kompensasjon til deltakerne er planlagt.

Eventuelle interessekonflikter for prosjektleder/-medarbeidere

Ingen sikre interessekonflikter

5.6 Publisering

Er det restriksjoner med hensyn til offentliggjøring og publisering av resultatene fra prosjektet? Nei

Redegjør for hvordan resultatene skal gjøres offentlig tilgjengelig

Resultatene vil bli formidlet både via vitenskapelige artikler og som abstracts (foredrag/posters) på nasjonale og internasjonale kongresser om barnekreft.

5.7 Håndtering av data etter prosjektslutt

Hvordan skal personopplysninger håndteres etter prosjektslutt?

Det planlegges at koplingsnøkkelen slettes ett år etter prosjektets avslutning, dvs ett år etter at siste publikasjon fra prosjektet er trykket.

6. Vedlegg

#	Type	Filnavn	Lagt inn dato
1.	Spørreskjema foreldre	Foreldre modul spørreskjema FysAk.pdf	03.05.16
2.	Spørreskjema	FysAk_spørreskjema_BARN_REK.pdf	03.05.16
3.	Forespørsel om deltakelse	Informasjonsskriv_endelig REK_03052016.pdf	03.05.16
4.	CV for prosjektleder	CV_Ruud.pdf	03.05.16
5.	Informasjon til barn og ungdom	Invitasjon barn og ungdommer WP2.pdf	03.05.16
6.	Intervjuguide	FysAk_intervjuguide_WP2.pdf	03.05.16
7.	Forskningsprotokoll	FysAk-barnekreft WP2_ prosjektbeskrivelse_endelig.pdf	03.05.16

7. Ansvarserklæring

Jeg erklærer at prosjektet vil bli gjennomført

☒ i henhold til gjeldende lover, forskrifter og retningslinjer

☒ i samsvar med opplysninger gitt i denne søknaden

☒ i samsvar med eventuelle vilkår for godkjenning gitt av REK eller andre instanser

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Anette Solli Karlsen	22845522	04.08.2016	2016/953/REK sør-øst A
			Deres dato:	Deres referanse:
			01.07.2016	

Vår referanse må oppgis ved alle henvendelser

Ellen Ruud
Kvinne- og barneklinikken, Oslo universitetssykehus HF

2016/953 Fysisk aktivitet hos barn og ungdommer etter kreftbehandling, FysAk Barnekreft

Forskningsansvarlig: Oslo universitetssykehus HF
Prosjektleder: Ellen Ruud

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 09.06.2016. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektbeskrivelse (redigert av REK)

Formålet med dette prosjektet er å undersøke selvrapportert og objektivt målt fysisk aktivitetsnivå hos barn og ungdom etter kreftbehandling.

Økt fokus på sunn livsstil er et gode for alle ungdommer og ikke minst de som har vært gjennom intensiv kreftbehandling. Barn og ungdommer som har gjennomgått slik behandling opplever ofte utfordringer med hverdagslige aktiviteter, som lek eller deltakelse i idrettslag og kroppsøvingstimer. Omfanget av problemet, om noen undergrupper har større problemer enn andre, mulige barrierer og behovet for oppfølging er lite undersøkt. Mer kunnskap på området kan bidra i arbeidet med å utforme målrettede tiltak til disse barna og ungdommene.

I prosjektet er det planlagt å inkludere 250 barn og ungdommer mellom 9 og 15 år, rekruttert ved poliklinisk kontroll på Seksjon for Kreftsykdommer hos Barn ved OUS-Rikshospitalet, minst 12 måneder etter avsluttet behandling.

Prosjektet er planlagt gjennomført som en tverrsnittstudie.

Deltakelse innebærer utfylling av spørreskjema og bruk av aktivitetsmålere. Spørreskjemaet omhandler livsstil, fysisk aktivitet, livskvalitet, mestring og kronisk trøtthet. Aktivitetsmålere er planlagt benyttet i en uke. De 20-30 første deltakerne vil bli invitert til kvalitative intervjuer for å kartlegge mulige barrierer for deltakelse i fysisk aktivitet og behovet for oppfølging.

I tillegg skal det innhentes opplysninger om kreftdiagnose, behandling, oppfølging og komplikasjoner fra journal.

Saksgang

Søknad om forhåndsgodkjenning ble behandlet av komiteen i møte den 09.06.2016, og det ble besluttet å utsette vedtak i saken.

Følgende inngikk i komiteens vurdering, jf. brev av 29.06.2016:

«*Etter komiteens syn er dette en viktig studie, der senvirkninger av kreftbehandling skal undersøkes. Deltakelse i prosjektet innebærer ubetydelig ulempe for barna utover den tid som medgår til studiebesøk, utfylling av spørreskjema og bruk av aktivitetsmåleren.*

Forskningsdeltakerens alder er 9-15 år. Selv om foreldre eller foresatte samtykke på vegne av barnet, legges det opp til at barnet selv skal ta stilling til egen deltakelse.

Forskning på personer uten selvstendig samtykkekompetanse er regulert av helseforskningslovens § 18. I følge Helseforskningsloven § 18 skal «slik forskning kun finne sted dersom:

a)eventuell risiko eller ulempe for personen er ubetydelig

b) personen selv ikke motsetter seg det

c) det er grunn til å anta at resultatene av forskningen kan være til nytte for den aktuelle personen eller forandre personer med samme aldersspesifikke lidelse, sykdom, skade eller tilstand

For mindreårige kreves det at tilsvarende forskning ikke kan gjennomføres på personer som ikke er mindreårige.»

Slik komiteen vurderer det er vilkårene om at forskningen ikke skal innebære risiko eller ulempe samt at personen selv ikke motsetter seg deltakelse oppfylt. Barna som deltar i prosjektet vil etter all sannsynlighet ikke ha direkte nytte av egen deltakelse, imidlertid vil de resultater som potensielt kan fremkomme i prosjektet potensielt ha stor nytteverdi for pasientgruppen.

Av disse grunner finner komiteen at prosjektet er forsvarlig å gjennomføre.

Imidlertid er det enkelte uklare punkter som komiteen ønsker tilbakemelding på før det tas stilling til godkjenning.

Slik komiteen forstår prosjektet, er formålet primært å beskrive deltakerens opplevelse av sitt personlige forhold knyttet til fysisk aktivitet. Noen variable som skal inngå eller beskrives i prosjektet går utover det. Eksempelvis inneholder spørreskjemaet til barna mange spørsmål som ikke handler om fysisk aktivitet, som for eksempel kosthold, livskvalitet, psykologiske faktorer og annet. Det fremkommer ikke av søknad eller protokoll hvordan disse variablene er relevante i forhold til studiens endepunkt. Det må i forhold til dette tydelig fremkomme av informasjonsskrivet hvilke opplysninger som skal innsamles til prosjektet.

I informasjonsskrivet til barna brukes følgende formulering: «Det blir spennende å se hvilken gruppe som er mest aktiv.» Etter komiteens syn er dette en noe uheldig formulering, som kan medføre at barna opplever at det er deres innsats som her blir målt. Det sies videre i informasjonsskrivet at det vil ta omtrent 15 minutter å utfylle spørreskjemaene. Etter komiteens syn vil dette trolig ta lengre tid, og det bes om at informasjonsskrivet revideres i tråd med dette.

Det fremkommer av søknaden at studiesykepleier skal ringe og purre på svar hos foreldre og foresatte, samt avtale tid for intervju. Komiteen har ingen innvendinger til at sykepleier tar kontakt for å avklare hvorvidt man er interessert i deltakelse eller ikke. Imidlertid kan det ikke godkjennes at det gjennomføres studierelaterte prosedyrer før samtykke er innhentet. Tid for intervju kan derfor ikke avtales før det signerte samtykkeskjema er innhentet.

Det bes om tilbakemelding på følgende merknader før det tas stilling til godkjenning av prosjektet:

1. *Det må redegjøres for hvordan de opplysninger man innsamler i prosjektet skal knyttes opp mot studiens endepunkt.*
2. *Informasjonsskrivet må revideres slik at det tydelig fremkommer hvilke endepunkter som skal undersøkes i prosjektet og hvor lang tid det er realistisk å bruke til utfylling av spørreskjemaene.*
3. *Det bes om at setningen: «Det blir spennende å se hvilken gruppe som er mest aktiv.» i informasjonsskrivet til barna omformuleres eller tas ut i sin helhet.*
4. *Det må legges opp til at det ikke gjøres avtaler om studierelaterte prosedyrer før signert samtykkeskjema er innhentet.*»

Prosjektleder har nå sendt tilbakemelding, mottatt 01.07.2016.

Det fremkommer av tilbakemeldingen at studiens primære endepunkt er måling av fysisk aktivitet hos ungdommer som tidligere har blitt behandlet for kreft. Sekundært inngår forklaringsmekanismer på og/eller konsekvenser av økt eller redusert aktivitetsnivå. Derfor er validerte spørsmål med tilgjengelig referansemateriale eller normmateriale om livskvalitet, kronisk utmattelse og personlighet inkludert i spørreskjemaet. Det antas at dette er faktorer som er assosiert med fysisk aktivitetsnivå i pasientgruppen. I tillegg skal assosiasjonen mellom fysisk aktivitet og andre livsstilsfaktorer som kan ha betydning for helse og seneffekter etter kreftbehandlingen undersøkes.

Informasjonsskrivet er revidert for å tydeliggjøre hvor lang tid det tar å utfylle spørreskjemaene og for å imøtekomme komiteens merknader. De aktuelle spørreskjemaene er revidert for å korte ned antall spørsmål.

Studierelaterte prosedyrer er endret slik at det ikke vil initieres studierelaterte aktiviteter før samtykke er innhentet.

Ny vurdering

Tilbakemeldingen er vurdert av komiteens leder på delegert fullmakt fra komiteen, og er å anse som tilfredsstillende i forhold til komiteens merknader.

Vedtak

Prosjektet godkjennes med hjemmel i helseforskningsloven §§ 9 og 33.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Godkjenningen gjelder til 31.12.2020.

Av dokumentasjonshensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Opplysningene skal oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en datafil. Opplysningene skal deretter slettes eller anonymiseres.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helseog omsorgssektoren».

Prosjektet skal sende sluttmelding på eget skjema, jf. helseforskningsloven § 12, senest et halvt år etter prosjektslutt.

Dersom det skal gjøres endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK, jf. helseforskningsloven § 11.

Klageadgang

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. helseforskningsloven § 10 tredje ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst A. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Med vennlig hilsen

Knut Engedal
Professor dr. med.
Leder

Anette Solli Karlsen
Komitesekretær

Kopi til:oushfdlgodkjenning@ous-hf.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Anne S. Kavli	22845512	09.10.2018	2016/953/REK sør-øst A
			Deres dato:	Deres referanse:
			05.10.2018	

Vår referanse må oppgis ved alle henvendelser

Ellen Ruud
Oslo universitetssykehus HF

2016/953 Fysisk aktivitet hos barn og ungdommer etter kreftbehandling, FysAk Barnekreft
Forskningsansvarlig: Oslo universitetssykehus HF
Prosjektleder: Ellen Ruud

Vi viser til søknad om prosjektendring datert 03.09.2018 samt til søknad om prosjektendring datert 05.10.2018 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst på fullmakt, med hjemmel i helseforskningsloven § 11.

Vurdering
REK har vurdert følgende endringer i prosjektet:

- Utvidelse av prosjektet å ikke bare gjelde Oslo og Bergen, men også tilsvarende datainnsamling i Danmark, Finland, Tyskland og Sveits. Data vil bli delt mellom disse samarbeidspartene etter regler fastsatt i kontrakter mellom institusjonene.
- Nye medarbeidere. Statistiker Corina Silvia Rueegg, Oslo universitetssykehus HF, Overlege, prof Päivi Lähteenmäki, Turku University Hospital, Finland, Forskningsleder Hannw Bækgaard Larsen, Rigshospitalet
- København Universitetshospital, Danmark, Forskningsleder Miriam Götte, Essen University Hospital, Tyskland, Overlege, prof Susi Kriemler, Universität Zürich, Sveits
- Reviderte informasjonsskriv
- Endring av spørreskjema. Det planlegges å legge til ett spørsmål om type fysisk aktivitet og noen spørsmål om motivasjon til fysisk aktivitet.

Komiteens leder har vurdert prosjektendringen og og godkjenner endringen på følgende vilkår.

- Komiteen forutsetter at informasjonsskriv til foresatte revideres i tråd med ny mal på REKs nettsider, slik at informasjonen som gis til deltakerne er forenlig med ny personopplysningslov. Revidert informasjonsskriv skal sendes inn til orientering.
- Kontrakter var ikke vedlagt, det bes om at disse ettersendes til orientering.
- Det forutsettes at kun avidentifiserte opplysninger deles med utlandet og at kodenøkkel forblir i Norge.
- Revidert spørreskjema sendes inn til orientering.

Vedtak

Komiteen godkjenner med hjemmel i helseforskningsloven § 11 annet ledd at prosjektet videreføres i samsvar med det som fremgår av søknaden om prosjektendring under forutsetning av at ovennevnte vilkår

oppfylles og i samsvar med de bestemmelser som følger av helseforskningsloven med forskrifter.

Vi gjør samtidig oppmerksom på at etter ny personopplysningslov må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Det må forankres i egen institusjon.

Dersom det skal gjøres ytterligere endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende ny endringsmelding til REK.

Av dokumentasjonshensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Opplysningene skal deretter slettes eller anonymiseres.

Opplysningene skal oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en datafil. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren».

Prosjektet skal sende sluttmelding til REK, se helseforskningsloven § 12, senest 6 måneder etter at prosjektet er avsluttet.

Klageadgang

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. helseforskningsloven § 10 tredje ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst A. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Vi ber om at alle henvendelser sendes inn på korrekt skjema via vår portal:

https://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på epost til: post@helseforskning.etikk.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Knut Engedal
Professor dr. med.
Leder

Anne S. Kavli
Seniorkonsulent

Kopi til: *oushfdlgodkjenning@ous-hf.no*

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Anne S. Kavli	22845512	12.04.2019	2018/739/REK sør-øst A
			Deres dato:	Deres referanse:
			03.03.2019	

Vår referanse må oppgis ved alle henvendelser

Truls Raastad
Norges idrettshøgskole

2018/739 Fysisk form hos barnekreftoverlevere

Forskningsansvarlig: Norges idrettshøgskole
Prosjektleder: Truls Raastad

Vi viser til søknad om prosjektendring datert 03.03.2019 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst på fullmakt, med hjemmel i helseforskningsloven § 11.

Vurdering

REk har vurdert følgende endringer i prosjektet:

- Nye blodprøver. Det søkes om å ta blodprøver av kontrollgruppen og analysere prøvene for ulike faktorerblant annet tradisjonelle metabolske risikofaktorer som HbA1c, HDL-kolesterol, total kolesterol og triglyserider.

Dette er allerede godkjent for barnekreftoverlevere, men ikke for kontroller.

- Klinisk undersøkelse av pubertetsstatus erstattes av egenrapportert pubertetsstatus for kontroller, og blir lagt til hos pasienter.

Informasjonsskrivet til kontrollene inneholder ingen informasjon om at prøver skal oppbevares i biobank. Komiteen legger derfor til grunn at disse prøvene analyseres innen 2 mnd og ber om at det legges til informasjon om hva som skjer med prøver i skrivet til kontrollgruppen.

Komiteens leder har vurdert prosjektendringene og har ingen forskningsetiske innvendinger mot endringene i prosjektet.

Vedtak

Komiteen godkjenner med hjemmel i helseforskningsloven § 11 annet ledd at prosjektet videreføres i samsvar med det som fremgår av søknaden om prosjektendring og i samsvar med de bestemmelser som følger av helseforskningsloven med forskrifter.

Vi gjør samtidig oppmerksom på at etter ny personopplysningslov må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Det må forankres i egen institusjon.

Dersom det skal gjøres ytterligere endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende ny endringsmelding til REK.

Av dokumentasjonshensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Opplysningene skal deretter slettes eller anonymiseres.

Opplysningene skal oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en datafil.

Prosjektet skal sende sluttmelding til REK, se helseforskningsloven § 12, senest 6 måneder etter at prosjektet er avsluttet.

Klageadgang

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. helseforskningsloven § 10 tredje ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst A. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Vi ber om at alle henvendelser sendes inn på korrekt skjema via vår portal: https://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på epost til: post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Knut Engedal
Professor dr. med.
Leder

Anne S. Kavli
Seniorkonsulent

Kopi til: *kristian.sollesnes@nih.no; Norges idrettshøgskole ved øverste administrative ledelse: postmottak@nih.no*

Invitasjon til deltakelse i forskningsprosjektet

"Fysisk aktivitet hos barn og ungdom etter kreftbehandling"

Bakgrunn og hensikt
Dette er et spørsmål til dere og deres barn om å delta i et forskningsprosjekt som har til hensikt å undersøke hvordan kreftsykdommen og behandlingen har påvirket ulike aspekter knyttet til barnets fysiske aktivitetsnivå. Kreft og kreftbehandling gir ofte flere bivirkninger som påvirker hverdagen og som kan vare en stund etter at behandlingen er avsluttet. Ved etterkontroller på sykehuset hører vi stadig om barn og ungdom som synes det er vanskelig å komme tilbake til det aktivitetsnivået de hadde før de ble syke. Det kan dreie seg om alt fra lek i hverdagen, deltagelse i kroppsøvingsfaget eller deltagelse i idrettslaget. Undersøkelser som kartlegger omfanget av dette problemet er ikke gjort i Norge tidligere. Vi vet derfor lite om det er enkelte undergrupper som har større problemer med å gjenopprette sitt aktivitetsnivå og vi vet lite om hvilke utfordringer og hindringer som påvirker aktivitetsnivået. Vi vet også lite om andre livsstilsfaktorer som kan påvirke helsetilstanden hos barn og ungdom etter kreftbehandling slik som kosthold, søvn og stillesittende tid foran elektroniske skjermer. Mer systematisk kunnskap om dette vil bidra til å lage mer målrettede tiltak som kan hjelpe barn og ungdom å returnere til hverdagen slik den var før sykdommen, i den grad det er mulig. Derfor kontakter vi nå barn og ungdom, og deres foresatte, som kommer på etterkontroll etter gjennomgått kreftbehandling på Rikshospitalet ved Oslo universitetssykehus. Barne- og ungdomsavdelingen på Rikshospitalet ved Oslo universitetssykehus, er ansvarlig for studien. Vi vil også samarbeide med universitetssykehus i Bergen (Haukeland), København (Danmark), Essen (Tyskland), Turku (Finland), Zurich (Sveits) om å samle inn data. Vi vil dele data mellom disse forskningsmiljøene, men alle data vil være avidentifiserte og behandles kun av fagpersonell knyttet til prosjektet.

Hva innebærer studien?
Studien består av tre deler og man kan velge å være med på en eller alle de tre delene. I **del I** vil vi be sønnen/datteren din om å fylle ut et elektronisk spørreskjema med spørsmål om blant annet fysisk aktivitetsnivå på fritiden, deltagelse i kroppsøvingstimene på skolen, hva som eventuelt har hindret han/henne i å være så fysisk aktiv som ønsket, barnets opplevde energinivå, kosthold og om hvordan hun/han har det generelt. Dere som foresatte vil også bli bedt om å svare på en forkortet foreldreversjon av samme spørreskjema. I **del 2** vil vi be barnet om å ha på en aktivitetsmåler i syv dager når han/hun er hjemme som så returneres til sykehuset i posten i en ferdig-frankert konvolutt. I **del 3** vil vi intervjue barna om deres erfaringer knyttet til fysisk aktivitet før og etter behandling, hva som eventuelt har vært til hinder for fysisk aktivitet og hvilke behov barnet har hatt for oppfølging i forhold til å gjenoppta fysisk aktivitet etter ferdigbehandling. Intervjuet er forventet å ta mellom 15 og 30 minutter. (mer informasjon se vedlegg A).

Mulige fordeler og ulemper
Fokus på en helsefremmende livsstil og fysisk aktivitet er positivt for alle ungdommer, og spesielt for de som tidligere har gjennomgått intensiv kreftbehandling. Det kan derfor være en fordel for dere å snakke gjennom ulike aspekter om fysisk aktivitet for å få et bevisst forhold til slike livsstilsvalg. Ved å delta i prosjektet vil barnet bli bedt om å svare spørreskjema og å

delta i et kort intervju. Barnet vil også bli bedt om å ha på seg en liten og lett aktivitetsmåler som er festet til et belte rundt livet i syv dager. Dette er ikke forbundet med noe ubehag. Deltakelse vil ikke medføre ekstra sykehusbesøk.

Hva skjer med informasjonen om deg/barnet ditt?
Informasjonen som registreres om barnet ditt, skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte identifiserende opplysninger (såkalte indirekte identifiserbare opplysninger). En kode knytter barnet ditt til barnets personlige opplysninger gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til barnet. Det vil ikke være mulig å identifisere barnet ditt i resultatene av studien når disse publiseres. Informasjonen som er registrert om barnet ditt vil oppbevares frem til forskningsprosjektet avsluttes og det ikke lenger er nødvendig å oppbevare kodenøkkelen som gjør det mulig å koble barnets identitet til opplysningene. Som regel kreves det at kodenøkkelen blir lagret en viss tid etter at prosjektet er avsluttet for mulig kontroll og etterprøvning. Kodenøkkelen vil slettes senest 31.12.2025.

Frivillig deltakelse
Det er helt frivillig å delta i studien. Dere står fritt til å velge å være med på en eller alle tre deler av studien. Dersom dere ikke ønsker å delta vil det **IKKE** få konsekvenser for den behandling og oppfølging dere får ved Barne- og ungdomsavdelingen ved Oslo

Universitetssykehus. Dersom dere ønsker å delta, undertegner dere samtykkeerklæringen på siste side. Begge foreldre må signere. På vegne av barnet, kan dere når som helst, og uten å oppgi noen grunn, trekke samtykke til å delta. Dette vil ikke få konsekvenser for barnets øvrige behandling verken nå eller senere. Dersom dere har spørsmål til studien eller senere ønsker å

trekke dere fra studien, kan dere kontakte prosjektkoordinator og studiesykepleier Elna Larsen, tlf: 23074560/47442720.

Kontaktopplysninger
Styringsgruppen for forskningsprosjektet består av:

Ellen Ruud, prof dr med, Seksjon for Pediatrisk Kreft og Blodsykdommer, OUS, tlf 23074560. Lene Thorsen, forsker PhD, Nasjonal kompetansetjeneste for seneffekter etter kreft, OUS, tlf 22934000. May Grydeland, 1. amanuensis PhD, Seksjon for fysisk prestasjonsevne, Norges idrettshøgskole, tlf 23262000. Hanne C Lie, forsker, Seksjon for Pediatrisk Kreft og Blodsykdommer, OUS, tel 22851466.

Ytterligere informasjon om studien finnes i vedlegg A – *Utdypende forklaring av hva studien innebærer.* Ytterligere informasjon om personvern, økonomi og forsikring finnes i vedlegg B – *Personvern, økonomi og forsikring.*

Samtykkeerklæringen følger etter vedlegg B.

Vedlegg A - Utdypende forklaring av hva studien innebærer

Hensikten med studien er å undersøke hvordan kreft og kreftbehandling påvirker ulike aspekter knyttet til fysisk aktivitet etter avsluttet kreftbehandling blant barn og ungdom mellom 9 og 15 år. Videre er hensikten å kartlegge hvilke utfordringer og behov barn og ungdommer møter når de skal være fysisk aktive. I forbindelse med etterkontrollen barnet ditt skal til, vil vi be han/hun om å svare på et spørreskjema, i tillegg vil noen bli spurt om å stille til et kort intervju. Barnet vil også bli utstyrt med en aktivitetsmåler som hun/han skal ha på seg i syv dager etter kontrollen, som så returneres til sykehuset i posten i en ferdig-frankert konvolutt. Kun relevante data som er knyttet til barnets diagnose og behandling vil bli hentet fra sykehusjournalen.

Spørreskjema
Når dere kommer til kontroll på Barne- og ungdomsavdelingen ved Rikshospitalet vil vi be sønnen/datteren din om å fylle ut et elektronisk spørreskjema. Det tar ca 15-20 minutter å svare på alle spørsmålene. En prosjektmedarbeider vil sitte sammen med han/henne for å svare på eventuelle spørsmål underveis. Spørreskjemaet inneholder spørsmål knyttet til ditt barns aktivitetsnivå på fritiden, hvordan barnet ditt opplever kroppsøvingsfaget, hva som eventuelt hindrer barnet ditt i å være så aktiv som det ønsker, barnets energinivå og hvordan han/hun har det generelt. Det er også spørsmål om andre livsstilsfaktorer som kosthold, søvn og tid foran elektroniske skjermer. Videre er det spørsmål om livskvalitet, personlighet (barnets sterke og svake sider) og trøtthet fordi vi ønsker å studere om det fysiske aktivitetsnivået kan sees i sammenheng med barnets opplevde livskvalitet, symptomer på kronisk utmattelse (fatigue) og/eller personlighetsfaktorer. Dere som foresatte vil bli bedt om å fylle ut en forkortet foreldreversjon av samme skjema som omhandler hvordan du opplever at ditt barn har det.

Aktivitetsmåler
I tillegg til å spørre barnet ditt om hvor aktiv han/hun er, ønsker vi å måle aktivitetsnivået med det som kalles et akselerometer. Akselerometeret registrerer alle bevegelsene barnet ditt gjør og intensiteten på disse. Det er et lite og lett instrument på størrelse med en fyrstikkeske som festes i et belte rundt livet. Vi har god erfaring med bruk av slike akselerometre blant andre barne- og ungdomsgrupper på samme alder. Dette skal barnet ditt ha på seg i syv dager etter at han/hun kommer hjem fra kontroll. Barnet skal ha det på seg hele dagen, med unntak av når han/hun bader/dusjer og tar den av når han/hun legger seg om kvelden. Når registreringen er ferdig skal akselerometeret legges i medbrakte adresserte og frankerte konvolutt og sendes tilbake til oss. Vi ber om at det gjøres så raskt som mulig slik at vi kan inkludere nye barn i studien.

Intervju
En del av barna vil bli spurt om de er villige til å la seg intervjue av en forsker. Dette intervjuet vil vare omlag 15-30 min og vil foregå på eller rett i nærheten av poliklinikken etter den vanlige konsultasjonen. Hensikten med intervjuet er å få informasjon om ditt barns erfaringer knyttet til fysisk aktivitet før og etter behandlingen. Videre vil vi gjerne høre hvilke utfordringer barnet ditt har møtt knyttet til fysisk aktivitet og om barnet ditt har mottatt

noe hjelp i forbindelse med dette. Vi ønsker å avdekke flest mulig temaer og utfordringer forbundet med fysisk aktivitet hos gruppen «barn og unge med en tidligere kreftdiagnose», som vi bør ta hensyn til ved planlegging av nye tiltak og studier på økt fysisk aktivitet. Intervjuene avsluttes når det ikke kommer opp flere nye temaer. Du som foresatt kan følge med til intervjuet om barnet så ønsk

Vedlegg B - Personvern, økonomi og forsikring

Personvern
Opplysninger som registreres om barnet ditt er knyttet til ulike aspekter av helsen, men først og fremst fysisk aktivitet. Noen barn vil bli intervjuet, alle fyller ut et spørreskjema og alle går med en aktivitetsmåler. Opplysning om diagnose og behandling vil hentes fra barnets sykehusjournal. Kun utvalgte personer i prosjektgruppa vil ha tilgang til datamaterialet. Oslo universitetssykehus ved administrerende direktør er databehandlingsansvarlig. Vi samarbeider med flere forskningsinstitusjoner, kun avidentifiserte data vil bli delt og behandlet av fag-personell knyttet til studien. Prosjektleder vil sikre at opplysningene blir ivaretatt på en trygg måte. Koden som knytter personidentifiserbare opplysninger til person vil ikke bli utlevert.

Rett til innsyn og sletting av opplysninger om deg/barnet ditt
Hvis dere sier ja til å delta i studien, har dere rett til å få innsyn i hvilke opplysninger som er registrert om barnet deres. Dere har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom barnet ditt trekkes fra studien, kan dere kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er brukt i publiserte vitenskapelige artikler.

Godkjenning
Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning (Saksnummer hos REK 2016/953/REK sør-øst A). Etter ny personopplysningslov har behandlingsansvarlig (OUS) og prosjektleder (prof. dr med Ellen Ruud) et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6a og 9a. Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

Økonomi
Studien finansieres primært gjennom forskningsmidler fra Norges forskningsråd. Den enkelte vil ikke få utgifter knyttet til deltakelse i studien.

Forsikring
Barnet ditt er forsikret i henhold til reglene i Pasientskadeloven og Norsk pasientskadeerstatning (NPE-ordningen).

Informasjon om utfallet av studien
Dere har rett til å få informasjon om utfallet/resultatet av studien.

Kontaktopplysninger
Dersom du har spørsmål til prosjektet kan du ta kontakt med prosjektleder Ellen Ruud (prof. Dr. med), Seksjon for Pediatrisk Kreft og Blodsykdommer, OUS, tlf 23074560/epost: elruud@ous-hf.no.

Du kan ta kontakt med institusjonens personvernombud dersom du har spørsmål om behandlingen av dine personopplysninger i prosjektet: personvern@ous-hf.no, eller telefon sentralbord OUS 91502770 .

Samtykke til deltakelse i studien

Jeg samtykker på vegne av mitt barn ..……..
at han/hun er villig til å delta i følgende deler av studien:

☐ Ja, mitt barn kan delta i Del 1: Spørreskjema

☐ Ja, mitt barn kan delta i Del 2: Måling av aktivitetsnivå hjemme

☐ Ja, mitt barn kan delta i Del 3: Intervju

(Signert av foresatt nr 1, dato) + foresattes navn med blokkbokstaver

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(Signert av foresatt nr 2, dato) + foresattes navn med blokkbokstaver

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

Invitasjon til deltakelse i forskningsprosjektet

"Fysisk aktivitet hos barn og ungdom etter kreftbehandling"

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i et forskningsprosjekt som har til hensikt å undersøke hvordan kreftsykdommen og behandlingen har påvirket ulike aspekter knyttet til det å være fysisk aktiv etter å ha blitt behandlet for en kreftsykdom. Kreft og kreftbehandling gir ofte flere bivirkninger som påvirker hverdagen og som kan vare en stund etter at behandlingen er avsluttet. Ved etterkontroller på sykehuset hører vi stadig at det kan være vanskelig å komme tilbake til det aktivitetsnivået man hadde før man ble syk. Det kan dreie seg om alt fra aktivitet i hverdagen, deltagelse i kroppsøvingsfaget eller deltagelse i idrettslaget. Undersøkelser som kartlegger omfanget av dette problemet er ikke gjort i Norge tidligere. Vi vet derfor lite om hvilke utfordringer og hindringer som påvirker aktivitetsnivået. Mer kunnskap om dette vil bidra til å kunne hjelpe barn og ungdom i å komme tilbake til hverdagen slik den var før sykdommen, i den grad det er mulig. Derfor kontakter vi nå ungdom, og deres foresatte, som kommer på etterkontroll etter gjennomgått kreftbehandling på Rikshospitalet ved Oslo universitetssykehus. Barne- og ungdomsavdelingen på Rikshospitalet ved Oslo universitetssykehus, er ansvarlig for studien.

Hva innebærer studien?
Studien består av et intervju med deg og dine foreldre om deres erfaringer knyttet til fysisk aktivitet før og etter behandling, hva som eventuelt har gjort det vanskelig å være fysisk aktivitet og om man har hatt behov for oppfølging i forhold til å gjenoppta fysisk aktivitet etter ferdigbehandling. Intervjuet er forventet å ta mellom 15 og 30 minutter. (mer informasjon se vedlegg A). En liste med spørsmål vi ønsker å diskutere danner grunnlaget for intervjuet.

Mulige fordeler og ulemper
Fokus på en helsefremmende livsstil og fysisk aktivitet er positivt for alle, og spesielt for de som tidligere har gjennomgått intensiv kreftbehandling. Det kan derfor være en fordel for dere å snakke gjennom ulike aspekter om fysisk aktivitet for å få et bevisst forhold til slike livsstilsvalg. Ved å delta i prosjektet vil du bli bedt om å delta i et kort intervju. Dette er ikke forbundet med noe ubehag. Deltakelse vil ikke medføre ekstra sykehusbesøk.

Hva skjer med informasjonen om deg/barnet ditt?
Selve intervjuet vil bli tatt opp på lydbånd slik at vi senere kan analysere innholdet på mest nøyaktig måte. Opptaket vil videre transkriberes, dvs vi skriver ned hva som ble sagt. Dette transkriptet er grunnlaget for videre analyser av temaer som blir diskutert under intervjuet. Ingen personidentifiserbare opplysninger vil bli inkludert i transkriptet. Informasjonen som registreres om deg, skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte identifiserende opplysninger (såkalte indirekte identifiserbare opplysninger). En kode knytter deg til dine personlige opplysninger gjennom en navneliste. Det er kun autorisert personell som har taushetsplikt knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg og det du har sagt i resultatene av studien når

disse publiseres. Informasjonen som er registrert om deg vil oppbevares frem til forskningsprosjektet avsluttes og det ikke lenger er nødvendig å oppbevare kodenøkkelen som gjør det mulig å koble din identitet til opplysningene. Som regel kreves det at kodenøkkelen blir lagret en viss tid etter at prosjektet er avsluttet for mulig kontroll og etterprøvning. Kodenøkkelen vil slettes senest 31.12.2025.

Frivillig deltakelse
Det er helt frivillig å delta i studien. Dersom du ikke ønsker å delta vil det **IKKE** få konsekvenser for den behandling og oppfølging du får ved Barne- og ungdomsavdelingen ved Oslo Universitetssykehus. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst, og uten å oppgi noen grunn, trekke samtykke til å delta. Dette vil ikke få konsekvenser for din øvrige behandling verken nå eller senere. Dersom du har spørsmål til studien eller senere ønsker å trekke dere fra studien, kan du kontakte prosjektkoordinator og studiesykepleier Elna Larsen, tlf: 23074560.

Ytterligere informasjon om studien finnes i vedlegg A – *Utdypende forklaring av hva studien innebærer* Ytterligere informasjon om personvern, økonomi og forsikring finnes i vedlegg B – *Personvern, økonomi og forsikring*

Samtykkeerklæringen følger etter vedlegg B

Vedlegg A - Utdypende forklaring av hva studien innebærer

Hensikten med studien er å undersøke hvordan kreft og kreftbehandling påvirker ulike aspekter knyttet til fysisk aktivitet etter avsluttet kreftbehandling blant barn og ungdom mellom 9 og 18 år. Videre er hensikten å kartlegge hvilke utfordringer og behov barn og ungdommer møter når de skal være fysisk aktive. I forbindelse med etterkontrollen ønsket vi å gjennomføre et kort intervju med deg og dine foreldre hver for dere. Kun relevante data som er knyttet til din diagnose og behandling vil bli hentet fra sykehusjournalen.

Intervjuet vil vare omlag 15-30 min og vil foregå på eller rett i nærheten av poliklinikken før eller etter den vanlige konsultasjonen. Sted og tid avtales på forhånd etter hva som passer dere best. Hensikten med intervjuet er å få informasjon om dine erfaringer knyttet til fysisk aktivitet før og etter behandlingen. Videre vil vi gjerne høre hvilke utfordringer du har møtt knyttet til fysisk aktivitet og om du har fått noe hjelp i forbindelse med dette. Vi ønsker å avdekke flest mulig temaer og utfordringer forbundet med fysisk aktivitet hos gruppen «barn og unge med en tidligere kreftdiagnose», som vi bør ta hensyn til ved planlegging av nye tiltak og studier på økt fysisk aktivitet. Intervjuene avsluttes når det ikke kommer opp flere nye temaer. Intervjuet vil bli tatt opp på digitale opptakere slik at vi senere kan analysere innholdet på mest nøyaktig måte.

Vedlegg B - Personvern, økonomi og forsikring

Personvern
Opplysninger som registreres om deg er knyttet til ulike aspekter av helsen, men først og fremst fysisk aktivitet. Opplysning om diagnose og behandling vil hentes fra din sykehusjournal. Kun utvalgte personer i prosjektgruppa vil ha tilgang til datamaterialet. Oslo universitetssykehus ved administrerende direktør er databehandlingsansvarlig.

Rett til innsyn og sletting av opplysninger om deg/barnet ditt
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du ønsker å trekke deg fra studien, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er brukt i publiserte vitenskapelige artikler.

Økonomi
Studien finansieres initialt gjennom forskningsmidler fra Helse Sør-Øst, og det vil bli søkt om ytterligere forskningsfinansiering fra andre finansieringskilder. Den enkelte vil ikke få utgifter knyttet til deltakelse i studien.

Forsikring
Du er forsikret i henhold til reglene i Pasientskadeloven og Norsk pasientskadeerstatning (NPE-ordningen).

Godkjenning
Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning (Saksnummer hos REK 2016/953/REK sør-øst A). Etter ny personopplysningslov har behandlingsansvarlig (OUS) og prosjektleder (prof. dr med Ellen Ruud) et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6a og 9a. Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

Kontaktopplysninger
Dersom du har spørsmål til prosjektet kan du ta kontakt med prosjektleder Ellen Ruud (prof. Dr. med), Seksjon for Pediatrisk Kreft og Blodsykdommer, OUS, tlf 23074560/epost: elruud@ous-hf.no.

Du kan ta kontakt med institusjonens personvernombud dersom du har spørsmål om behandlingen av dine personopplysninger i prosjektet: personvern@ous-hf.no, eller telefon sentralbord OUS 91502770 .

Informasjon om utfallet av studien
Du har rett til å få informasjon om utfallet/resultatet av studien.

Samtykke til deltakelse i studien

Jeg, _____ (ditt navn),

er villig til å delta i studien:

.

(Din signatur)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

INFORMASJONSSKRIV TIL BARN UNDER 12 ÅR:

FYSISK FORM HOS BARNEKREFTOVERLEVERE

HVORFOR BLIR DU SPURT OM Å VÆRE MED?

Vi spør om du vil delta i dette forskningsprosjektet fordi vi ønsker å få vite mer om hvordan kreftbehandling kan påvirke formen din. Kreftbehandlingen du har gjennomgått kan påvirke kroppen på mange ulike måter og mange barn og ungdom i din situasjon opplever at de fort blir slitne. Hvis vi får mer kunnskap om dette kan vi sette i gang tiltak for å hjelpe barn og ungdom til å være så fysisk aktive som de ønsker å være. På den måten kan vi kanskje hjelpe barn og ungdom til å få bedre fysisk form under og etter behandlingen.

HVA VIL SKJE DERSOM DU DELTAR?

Studien vil foregå på to forskjellige dager med noen ukers mellomrom. Første oppmøte er på Rikshospitalet i forbindelse med en av dine vanlige oppfølgingsundersøkelser etter kreftbehandlingen. Det vil bli tatt blodprøve, målt høyde, lengde, vekt og blodtrykk, og legen din vil gjøre undersøkelser du kjenner fra før, som også inneholder vurdering av hvor langt du har kommet i puberteten (legen ser blant annet på utvikling av pupper og hår på tissen).

Samme dag blir det en undersøkelse av hjertet ditt med ultralyd og en undersøkelse av lungene og hvor godt du puster. Hjerteundersøkelsen foregår ved at du ligger på ryggen og en hjertelege "kikker" på hjertet ditt ved å holde ultralydhodet mot brystkassen din (se bilde til høyre). I tillegg vil de se på hjerterytmen din ved å feste elektroder på brystkassen. Hjerteundersøkelsen tar ca. 30 minutter.

Bilde av hjerteundesøkelse med ultralyd

Pustekapasiteten din vil bli målt ved at du puster på forskjellige måter inn i ett munnstykke. Lungefunksjonsmålingene gir oss et mål på hvor raskt du klarer å puste ut, hvor store lungene dine er og hvordan oksygen overføres fra lungene til blodet. Denne undersøkelsen vil ta ca. 30 min. Totalt vil alle undersøkelsene på Rikshospitalet denne dagen ta 3-5 timer avhengig av hvilke andre rutineundersøkelser som er planlagt.

Bilde av utstyret som brukes til å måle lungefunksjon

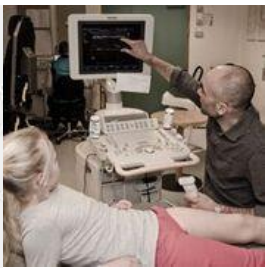
På den andre testdagen skal du møte sammen med en klassekamerat/venn og far eller mor. Klassekameraten/vennen din skal gjennomføre akkurat de samme testene som deg. Denne dagen møter dere på Ullevål sykehus der det skal gjennomføres tre enkle undersøkelser av hvordan nervene kontrollerer muskler og sanseinntrykk (blant annet hvordan du oppfatter trykk og varme mot huden). Disse undersøkelsene vil totalt ta ca. 1,5 timer for deg og vennen din som testes sammen.

- Undersøkelse 1: Nevrografi: Nevrografi betyr at vi setter svak strøm i huden over ulike nerver i armene og bena for å se hvordan muskelen reagerer. Under undersøkelsen kan det gjøre litt vondt under strømstøtene, men du kan si stopp når du vil og da vil vi stoppe, til du synes det er greit å starte igjen.
- Undersøkelse 2: Termotest: Her vil vi undersøke om nerver som kjenner om det er varmt eller kaldt virker som de skal. Vi undersøker ved hjelp av en metallplate som kan varmes opp. Denne metallplaten fester vi utenpå huden. Vi undersøker i håndflaten, på fotryggen (oppå foten), på leggen og låret. Vi vil se på hvor fort du kjenner at det blir varmt. Det gjør vi ved at du trykker på en knapp når du kjenner at det blir varmere. Termotesten kan oppleves som litt ubehagelig, men dette går fort over. Du kan også si stopp når du ønsker det.
- Undersøkelse 3: Nevrologisk undersøkelse: Her vil vi undersøke nerver som sender signaler fra hjernen til musklene (motorikk), og nerver som sender signaler fra kroppen til hjernen (sanseinntrykk). Undersøkelsen skjer ved at vi spør deg noen spørsmål om hvordan du opplever at disse nervene fungerer (om du føler du har kontroll over muskler og sanseinntrykk). Vi vil også undersøke hvordan du oppfatter ulike typer berøring (å bli tatt på). Til slutt vil vi undersøke hvor sterke musklene dine er i hender og føtter, og teste refleksene dine.

Når dere er ferdige med undersøkelsene på Ullevål sykehus vil dere bli kjørt opp til Norges idrettshøgskole (NIH) der resten av de fysiske målingene gjennomføres. Kjøreturen fra Ullevål til NIH tar ca. 10 minutter. På NIH skal dere gjennomfører undersøkelsene for kondisjon (hvor god form du er i), muskelstyrke, spenst, blodvolum (hvor mye blod du har i kroppen) og kroppssammensetning. Dere vil totalt bruke ca. 3 timer på disse undersøkelsene, og dere vil få mat og drikke underveis.

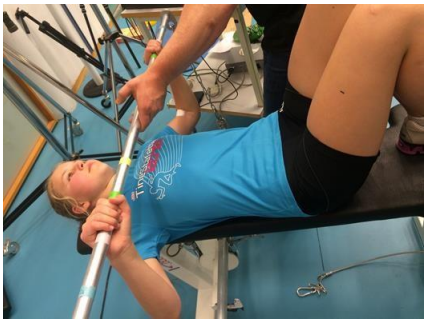
- For å se hva kroppen din består av (kroppssammensetning) vil vi gjøre en dexascan undersøkelse (minner om en vanlig røntgenundersøkelse) for å beregne muskelmasse, fettmasse og beinmasse. Deretter skal vi måle tykkelsen på én lår- og én armmuskel ved hjelp av ultralyd. Dexascan tar 15 minutter og det samme gjør ultralydundersøkelsen av bein- og armmuskel.

Bilde av dexascan



Bilde av ultralydundersøkelse av lår og arm

- Styrke i overkroppen måles ved at du ligger på en benk og presser armene alt du orker mot en fast stang (benkpress). I tillegg måler vi håndgrepsstyrken din ved at du klemmer så hard du kan på et håndtak. Styrken i beina måles ved at du sitter og presser leggen mot en fast plate (knestrekk). På alle testene tar i alt du orker i 2-3 sekunder og gjentar dette 2-3 ganger med ett minutts pause mellom hvert forsøk. Til slutt vil vi telle hvor mange ganger du klarer å reise deg opp og sette deg ned på en stol i løpet av 1 min. Totalt tar styrketestene ca. 20 min.



Styrketest overkropp

Styrketest bein

- Kondisjonen din vil bli målt mens du går/løper på en tredemølle. Farten på tredemøllen starter rolig, og økes deretter gradvis til du ikke orker mer. Under testen har du på en maske som samler opp all luften som pustes ut slik at vi kan måle hvor mye oksygen kroppen din tar opp. Du kommer merke at du blir ganske sliten på slutten av denne testen (puster tungt). Undersøkelsen vil ta ca. 20 minutter, men det er kun på slutten at du blir veldig sliten. Under denne undersøkelsen vil du ha på deg utstyr som gjør at vi kan følge med på blodtykket ditt og hvordan hjertet slår underveis.

- For å kunne måle hvor mye blod du har i kroppen skal du puste i et munnstykke i et par minutter. Samtidig med testen skal det også tas en blodprøve fra armen din samt to små fingerstikk. Resultatene fra disse blodprøvene brukes til å regne ut blodvolumet ditt. Du vil få bedøvelseskrem på armen og fingrene, slik at du ikke merker når vi stikker deg.

Bilde av utstyret som brukes til å måle blodvolum

Når du er ferdig med alle undersøkelsene vil du få utdelt en aktivitetsmåler som du skal ha på deg i én uke. Dette er den samme aktivitetsmåleren som du har gått med tidligere, og målingen gjennomføres på akkurat samme måte som sist. Du skal også fylle ut et kort spørreskjema om fysisk aktivitet og pubertet på en Ipad og det tar 10-15 minutter. Dette kan du gjøre i pausene mellom undersøkelsene.

HVA VIL SKJE DERSOM DU IKKE DELTAR

Det er frivillig å delta i prosjektet og du kan når som helst og uten å oppgi noen grunn trekke deg fra studien.

INFORMASJONSSKRIV TIL UNGDOM 12-18 ÅR:

FYSISK FORM HOS BARNEKREFTOVERLEVERE

BAKGRUNN OG HENSIKT

Vi spør om du vil delta i dette forskningsprosjektet fordi vi ønsker å få vite mer om hvordan kreftbehandling kan påvirke formen din. Kreftbehandlingen du har gjennomgått kan påvirke kroppen på mange ulike måter og mange barn og ungdom i din situasjon opplever at de fort blir slitne. Hvis vi får mer kunnskap om dette kan vi sette i gang tiltak for å hjelpe barn og ungdom til å være så fysisk aktive som de ønsker å være. På den måten kan vi kanskje hjelpe barn og ungdom til å få bedre fysisk form under og etter behandlingen.

HVA INNEBÆRER STUDIEN?

Studien vil foregå på to forskjellige dager med noen ukers mellomrom. Første oppmøte er på Rikshospitalet i forbindelse med en vanlig oppfølgingsundersøkelse. Det vil som vanlig bli tatt en blodprøve, målt høyde, vekt og blodtrykk, og den kjente legen din vil gjennomføre den vanlige undersøkelsen. I tillegg vil legen gjøre en vurdering av hvor langt du har kommet i puberteten.

Samme dag blir det hjerteundersøkelse med ultralyd og en undersøkelse av lungefunksjon. Hjerteundersøkelsen foregår ved at du ligger på ryggen og en hjertelege "kikker" på hjertet ditt ved å holde ultralydhodet mot brystkassen din (se bilde til høyre). I tillegg vil de se på hjerterytmen din ved å feste elektroder på brystkassen. Hjerteundersøkelsen tar ca. 30 minutter.

Bilde av hjerteundesøkelse med ultralyd

Lungefunksjon vil bli målt ved at du du puster på forskjellige måter inn i ett munnstykke. Lungefunksjonsmålingene gir oss et mål på hvor raskt du klarer å puste ut, hvor store lungene dine er og hvordan oksygen overføres fra lungene til blodet. Denne undersøkelsen vil ta ca. 30 min. Du vil totalt bruke 3-5 timer på Rikshospitalet denne dagen avhengig av hvilke andre rutineundersøkelser som er planlagt.

Bilde av utstyret som brukes til å måle lungefunksjon

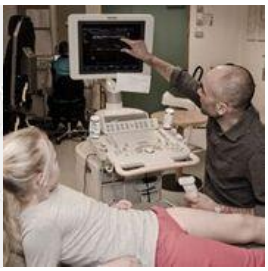
På den andre testdagen kan du møte sammen med en klassekamerat/venn og far eller mor. Denne dagen møter dere på Ullevål sykehus der det skal gjennomføres tre enkle undersøkelser av nervesystemets kontroll på muskulatur og sanseinntrykk (hvordan du bl.a. oppfatter trykk og varme mot huden). Disse undersøkelsene vil totalt ta ca. 1 time for dere to som testes sammen.

- Undersøkelse 1: Nevrografi: Nevrografi betyr at vi setter svak strøm i huden over ulike nerver i armene og bena for å se hvordan muskelen reagerer. Under undersøkelsen kan det gjøre litt vondt under strømstøtene, men du kan si stopp når du vil og da vil vi stoppe, til du synes det er greit å starte igjen.
- Undersøkelse 2: Termotest: Her vil vi undersøke om nerver som kjenner om det er varmt eller kaldt virker som de skal. Vi undersøker ved hjelp av en metallplate som kan varmes opp. Denne metallplaten fester vi utenpå huden. Vi undersøker i håndflaten, på fotryggen (oppå foten), på leggen og låret. Vi vil se på hvor fort du kjenner at det blir varmt. Det gjør vi ved at du trykker på en knapp når du kjenner at det blir varmere. Termotesten kan oppleves som litt ubehagelig, men dette går fort over. Du kan også si stopp når du ønsker det.
- Undersøkelse 3: Nevrologisk undersøkelse: Her vil vi undersøke nerver som sender signaler fra hjernen til musklene (motorikk), og nerver som sender signaler fra kroppen til hjernen (sanseinntrykk). Undersøkelsen skjer ved at vi spør deg noen spørsmål om hvordan du opplever at disse nervene fungerer (om du føler du har kontroll over muskler og sanseinntrykk). Vi vil også undersøke hvordan du oppfatter ulike typer berøring (å bli tatt på). Til slutt vil vi undersøke hvor sterke musklene dine er i hender og føtter, og teste refleksene dine.

Når dere er ferdige med Undersøkelse på Ullevål sykehus vil dere bli kjørt opp til Norges idrettshøgskole (NIH) der de fysiske Undersøkelse skal gjennomføres. Kjøreturen fra Ullevål til NIH tar ca. 10 minutter. På NIH skal dere gjennomfører målinger for kondisjon (det maksimale oksygenopptaket), muskelstyrke, spenst, blodvolum og kroppssammensetning. Undersøkelsene vil totalt ta ca. 3 timer, og dere vil få mat og drikke underveis.

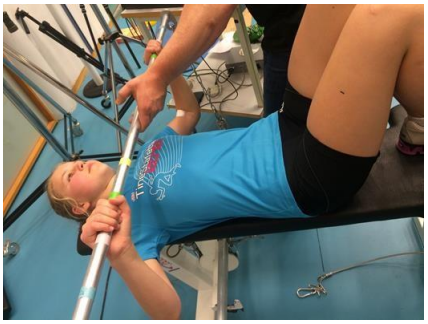
- For å se hva kroppen din består av (kroppssammensetning) vil vi gjøre en dexascan undersøkelse (minner om en vanlig røntgenundersøkelse) for å beregne muskelmasse, fettmasse og beinmasse. Deretter skal vi måle tykkelsen på én lår- og én armmuskel ved hjelp av ultralyd. Dexascan tar 10 minutter og det samme gjør ultralydundersøkelsen av bein- og armmuskel.

Bilde av dexascan



Bilde av ultralydundersøkelse av lår og arm

- Styrke i overkroppen måles ved at du ligger på en benk og presser armene alt du orker mot en fast stang (benkpress). I tillegg måler vi håndgrepsstyrken din ved at du klemmer så hard du kan på et håndtak. Styrken i beina måles ved at du sitter og presser leggen mot en fast plate (knestrekk). På alle testene tar i alt du orker i 2-3 sekunder og gjentar dette 2-3 ganger med ett minutts pause mellom hvert forsøk. Til slutt vil vi telle hvor mange ganger du klarer å reise deg opp og sette deg ned på en stol i løpet av 1 min. Totalt tar styrketestene ca. 20 min.



Styrketest overkropp

Styrketest bein

- Kondisjonen din vil bli målt mens du går/løper på en tredemølle. Farten på tredemøllen starter rolig, og økes deretter gradvis til du ikke orker mer. Under testen har du på en maske som samler opp all luften som pustes ut slik at vi kan måle hvor mye oksygen kroppen din tar opp.. Du kommer merke at du blir ganske sliten på slutten av denne testen (puster tungt). Undersøkelsen vil ta ca. 20 minutter, men det er kun på slutten at du blir veldig sliten. Under denne undersøkelsen vil du ha på deg utstyr som gjør at vi kan følge med på blodtykket ditt og hvordan hjertet slår underveis.

Kondisjonstest på tredemølle

- For å kunne måle hvor mye blod du har i kroppen skal du puste i et munnstykke i et par minutter. Samtidig med testen skal det også tas en blodprøve fra armen din samt to små fingerstikk. Resultatene fra blodprøvene brukes til å regne ut blodvolumet ditt og vi ser på metabolske verdier i blodet. Du vil få bedøvelseskrem på armen og fingrene, slik at du ikke merker når vi stikker deg.

Bilde av utstyret som brukes til å måle blodvolum

Når du er ferdig med alle undersøkelsene vil du få utdelt en aktivitetsmåler som du skal ha på deg i én uke. Dette er den samme aktivitetsmåleren som du har gått med tidligere, og målingen gjennomføres på akkurat samme måte som sist. Du skal også fylle ut et kort spørreskjema om fysisk aktivitet og pubertet på en IPad og det tar 10-15 minutter. Dette kan du gjøre i pausene mellom undersøkelsene.

MULIGE FORDELER OG ULEMPER

Ved å være med på denne undersøkelsen vil du lære litt om kroppen din og hvordan forskning foregår. Under den nevrologiske undersøkelsen settes det svak strøm i huden og disse strømstøtene kan gjøre litt vondt. Termotesten innebærer varmestimulering som kan oppleves som lett til moderat, men kortvarig ubehag. I forbindelse med måling av blodvolum må vi ta en blodprøve fra en armene. Vi bedøver huden der vi skal ta blodprøven, men det vil likevel gjøre litt vondt. Ingen øvrige undersøkelser er forbundet med smerte. Måling av maksimalt oksygenopptak ved løp på tredemølle kan oppleves som slitsomt, og det kreves at du løper til du blir ganske sliten. På oppfølgingsundersøkelsen på Barneavdeling for kreft og blodsykdommer kan det bli gjort funn som får følger for den videre medisinske oppfølgingen/behandlingen av deg. Videre oppfølging av eventuelle funn vil følge de vanlige retningslinjer og rutiner på avdelingen uavhengig av forskningsprosjektet. Ingen av undersøkelsene på testdag 1 på Rikshospitalet ansees som rene forskningsundersøkelser (med unntak av blod til den generelle barnekreftbiobanken), og pasientene har rett til fullt innsyn i resultatene, som ved andre nødvendige helseundersøkelser. Dersom du ønsker å gi blod til den generelle forskningsbanken vil denne blodprøven lagres i forskningsbiobanken "OUS Barnebiobank – barnekreft (REK nr 2016/943), og vil brukes til annen forskning på barnekreft.

HVA SKJER MED PRØVENE OG INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til opplysninger gjennom en navneliste.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om barnet ditt blir behandlet på en sikker måte. Informasjon om deg ditt vil bli anonymisert eller slettet senest fem år etter prosjektslutt.

DELTAKELSE

Det er frivillig å delta i prosjektet. Du kan når som helst og uten å oppgi noen grunn trekke deg fra studien. Dette vil ikke få konsekvenser for videre behandling. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte PostDoc Elisabeth Edvardsen (tlf: 23262391, epost: elisabeth.edvardsen@nih.no).

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET FOR DITT BARN

FYSISK FORM HOS BARNEKREFTOVERLEVERE

Dette er et spørsmål til deg som foresatt om ditt barn kan delta i et forskningsprosjekt som skal undersøke fysisk form hos barnekreftoverlevere i alderen 10 til 18 år. Vi skal undersøke dette i en gruppe barnekreftoverlevere og sammenligne med barn i samme alder som ikke har vært igjennom kreftbehandling (kontroller). Hvis du samtykker til at ditt barn kan delta i denne studien kan dere, hvis dere ønsker, invitere med en klassekamerat (eller venn) av samme kjønn og alder som ditt barn til testdagen. Hvis foresatte til klassekameraten/vennen og vennen selv bekrefter at de ønsker å delta i undersøkelsen og de godkjenner at vi kan få e-post adresse/postadresse fra dere, vil vi i prosjektledelsen sende informasjon og formell forespørsel om deltakelse i studien til de foresatte for det aktuelle barnet og ha den videre kontakten.

Barnekreftbehandling kan påvirke kroppen på mange måter. Under aktiv behandling reduseres vanligvis den fysiske formen, og det kan ta tid før man henter seg inn igjen etter behandlingsslutt. I tillegg kan det for noen være utfordrende å ta opp igjen de fysiske aktivitetene man var med på tidligere. Redusert aktivitetsnivå og seineffekter etter behandling kan påvirke barnekreftoverlevernes fysiske form og helse mange år etter behandlingsslutt. Det er disse utfordringene knyttet til fysisk form og fysisk aktivitet vi ønsker å undersøke i denne studien for eventuelt å sette inn tiltak som bedrer formen for ungdomsgruppen på kort og lang sikt.

Før barnet ditt kan testes på fysisk form, vil det i forbindelse med en vanlig oppfølgingskontroll gjennomgå utvidete undersøkelser av hjerte, lunger, pubertetsnivå og nervefunksjon på Oslo universitetssykehus. Formålet med disse undersøkelsene er både for å forsikre oss om at det er trygt for barnet ditt å gjennomgå de fysiske testene på Norges idrettshøgskole og for å få viktig bakgrunnsinformasjon for å tolke testresultatene.

HVA INNEBÆRER PROSJEKTET?

Studien vil foregå på to forskjellige dager med noen ukers mellomrom. Første oppmøte er i forbindelse med en vanlig oppfølgingsundersøkelse ved poliklinikken/dagposten på Barneavdeling for kreft og blodsykdommer på Rikshospitalet. Undersøkelsene kombineres med rutinekontrollen på Barnepoliklinikken. Sykepleierne vil måle høyde, vekt og blodtrykk, og den kjente legen deres vil gjøre vanlig full klinisk undersøkelse som også inkluderer vurdering av pubertetsutviklingen (Tanner stadium). Som ved andre kontroller blir det rutinemessig blodprøvetaking, og vi kommer til å be om tillatelse til å ta 3-4 ml ekstra blod til en generell forskningsbiobank for framtidig barnekreftforskning (dere får eget informasjonsskriv om det).

Samme dag blir det hjerteundersøkelse med ultralyd (Ekko) og en enkel EKG-undersøkelse for å se på hjerterytme. Lungefunksjon vil bli målt ved at man puster rolig ut og inn i et munnstykke et par ganger før lungene fylles maksimalt med luft for så å puste hardt og lenge ut. Dersom man ved hjerte- eller lungeundersøkelsene har funn som tilsier at det er risikabelt å gjøre testingen på idrettshøgskolen, vil pasienten få beskjed og nødvendige medisinske tiltak settes i gang. Det blir da ikke aktuelt å fortsette i studien. Undersøkelsene på første oppmøtedag vil til sammen ta 3-5 timer, avhengig av hvilke andre rutineundersøkelser som er planlagt samme dag.

På den andre testdagen møter ditt barn sammen med klassekameraten/vennen til de fysiske testene. Dagen starter på Nevrofysiologisk laboratorium på Ullevål sykehus der det gjennomføres tre enkle undersøkelser av nervesystemets kontroll på muskulatur og sanseinntrykk (hvordan vi bl.a. oppfatter trykk og varme mot huden). Dette er standard kliniske undersøkelser, og det vil totalt ta ca. 1,5 time for de to barna som kommer til test samtidig.

1. Nevrografi: Formålet med undersøkelsen er å måle de tykke nervefibrene, både utoverledende (til muskler) og innoverledende (sanseinntrykk). Ved nevrografi setter vi svak strøm i huden over ulike nerver i armene og bena og registrerer effekt på muskelen ved hjelp av en elektrode festet til huden. Vi setter også strøm i huden og registrerer i huden over visse nerver. Det er ikke risiko for varige skader av denne undersøkelsen. Under undersøkelsen kan det kjennes noe ubehag under strømstøtene. Metoden har vært rutineundersøkelse på pasienter i flere tiår og gjennomføres vanligvis uten problemer.
2. Termotest: Formålet med undersøkelsen er å kartlegge funksjonen til tynne nervefibre som har med temperaturoppfattelse å gjøre. Vi undersøker ved hjelp av en metallplate som kan varmes opp. Denne metallplaten fester vi utenpå huden. Vi undersøker i håndflate, fotrygg, legg og lår. Vi vil se på tersklene for oppfattelse av varme og du selv trykker på en knapp når du kjenner temperaturendring. Termotesten innebærer varmestimulering som kan oppleves som lett til moderat, men kortvarig ubehag.
3. Nevrologisk undersøkelse: Formålet med den nevrologiske undersøkelsen er å vurdere om pasienten har symptomer eller tegn på nedsatt funksjon i nerver som formidler signaler til muskler (motorikk), eller i nerver som leder signaler innover (sanseinntrykk), eller i nerver som tilhører det autonome nervesystemet. Undersøkelsen skjer dels ved at det stilles noen spørsmål om vedkommende har aktuelle symptomer, dels ved at det undersøkes for respons på ulike typer berøring og for muskelstyrke i hender og føtter samt at det gjøres testing av dype senereflekser. Undersøkelsen er ikke smertefull og innebærer ikke risiko.

På Norges idrettshøgskole gjennomfører barna testene for kondisjon (det maksimale oksygenopptaket), muskelstyrke, spenst, blodvolum og kroppssammensetning. Testene vil totalt ta ca. 3 timer og barna vil få enkel servering underveis (mat og drikke).

- Kroppssammensetning for beregning av muskelmasse, fettmasse og beinmasse vil bli målt ved en dexascan (DXA) undersøkelse (minner om en vanlig røntgenundersøkelse). Dessuten skal vi måle tykkelsen på én lår- og én armmuskel ved hjelp av ultralyd.
- Styrke måles ved å ligge på en benk og presse armene mot en fast stang (isometrisk benkpress), ved å klemme så hardt man klarer mot et håndtak (håndgrepsstyrke), og ved å sitte og presse leggen mot en fast plate (isometrisk knestrekk). I tillegg vil vi telle hvor mange ganger barnet klarer å reise seg opp og ned fra en stol på 1 min.
- Det maksimale oksygenopptaket vil bli målt mens man løper på en tredemølle. Hastigheten økes gradvis til man blir ganske sliten. Under testen har man på en maske på som samler opp all luften som pustes ut slik at vi kan måle oksygenopptaket. Barna har på seg elektroder og blodtrykksmåler under denne undersøkelsen slik at vi kontinuerlig følger med på hjertefrekvens og blodtrykk.
- Måling av blodvolum skjer ved at man puster i et munnstykke forbundet med et kammer med oksygen tilsatt en liten mengde karbonmonoksid (som ofte kalles CO). Samtidig med testen skal det tas en blodprøve fra en armvene for måling av blodsammensetning og metabolske verdier. Resultatene fra denne blodprøven brukes sammen med Hb-massen til å regne ut blodvolumet.

I prosjektet vil vi innhente og registrere opplysninger om barnet ditt. Opplysningene som blir registrert er:

1. Resultater fra den klinisk legeundersøkelsen med blodprøveresultater og bakgrunnsvariabler om kreftsykdom, behandling og komplikasjoner
2. Resultater fra hjerteundersøkelsen
3. Resultater fra undersøkelsen om lungefunksjon
4. Resultater fra den nevrologiske undersøkelsen
5. Resultater fra aktivitetsmålingen
6. Resultater fra måling av kroppssammensetning

7. Resultater fra måling av muskelstyrke og spenst
8. Resultater fra måling av kondisjon (maksimalt oksygenopptak)
9. Resultater fra måling av blodvolum og metabolske verdier
10. Spørreskjema: I pausene mellom undersøkelsene vil barnet fylle ut et spørreskjema om fysisk aktivitet, trøtthet og motivasjon for fysisk aktivitet på en Ipad. Dette er en forenklet versjon av spørreskjemaet de fylte ut i FysAk Barnekreft prosjektet. I tillegg er det 4 enkle spørsmål om pubertetsstatus (5 for jenter).

Etter at alle undersøkelsene er gjennomført på Norges idrettshøgskole får dere utlevert en aktivitetsmåler lik den som ble brukt FysAk Barnekreft prosjektet. Den skal barnet ha på seg i én uke og aktivitetsmåleren sendes deretter i posten tilbake i ferdig frankert konvolutt.

Alle data lagres i en sikker database ved Norges idrettshøgskole (NIH). Data som samles inn ved Oslo Universitetssykehus (punkt 1-4) registreres ved OUS og overføres via papir til databasen ved NIH.

MULIGE FORDELER OG ULEMPER

Ved å være med på denne undersøkelsen vil barna lære litt om kroppen sin og hvordan forskning foregår. Under den nevrologiske undersøkelsen settes det svak strøm i huden og disse strømstøtene kan for noen oppleves som ubehagelig. Termotesten innebærer varmestimulering som kan oppleves som lett til moderat, men kortvarig ubehag. I forbindelse med måling av blodvolum må vi ta en blodprøve fra armvene. Vi bedøver huden der vi skal ta blodprøven slik at det ikke skal gjøre vondt. Ingen øvrige undersøkelser er forbundet med smerte. Måling av maksimalt oksygenopptak ved løp på tredemølle kan oppleves som slitsomt, og det kreves at de løper til de blir ganske slitene. På oppfølgingsundersøkelsen på Barneavdeling for kreft og blodsykdommer kan det bli gjort funn som får følger for den videre medisinske oppfølgingen/behandlingen av ditt barn. Videre oppfølging av eventuelle funn vil følge de vanlige retningslinjer og rutiner på avdelingen uavhengig av forskningsprosjektet. Ingen av undersøkelsene på testdag 1 på Rikshospitalet ansees som rene forskningsundersøkelser (med unntak av blod til den generelle barnekreftbiobanken), og pasientene har rett til fullt innsyn i resultatene, som ved andre nødvendige helseundersøkelser.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker at barnet ditt skal delta, undertegner du samtykkeerklæringen på siste side. Vi trenger samtykke fra begge foreldrene. Du kan når som helst og uten å oppgi noen grunn trekke samtykket til at ditt barn skal delta i studien. Dette vil ikke få konsekvenser for videre behandling. Dersom du trekker barnet ditt fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte PostDoc Elisabeth Edvardsen (tlf: 23262391, epost: elisabeth.edvardsen@nih.no).

HVA SKJER MED INFORMASJONEN OM BARNET DITT?

Informasjonen som registreres om barnet ditt skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter barnet til opplysninger gjennom en navneliste.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om barnet ditt blir behandlet på en sikker måte. Informasjon om barnet ditt vil bli anonymisert eller slettet senest fem år etter prosjektslutt.

Etter ny personopplysningslov har behandlingsansvarlig Norges idrettshøgskole og prosjektleder Truls Raastad et selvstendig ansvar for å sikre at behandlingen av ditt barns opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6a og 9a. Du har rett til å klage på behandlingen av deres opplysninger til Datatilsynet.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet kan du kontakte prosjektleder Truls Raastad, tlf.: 23262328, mail: truls.raastad@nih.no. Du kan ta kontakt med institusjonens personvernombud dersom du har spørsmål om behandlingen av ditt barns personopplysninger i prosjektet, Karine Justad, e-post: karine.justad@nih.no, tlf. 232 62 089.

DELING AV DATA OG OVERFØRINGER TIL UTLANDET

Ved å delta i prosjektet, samtykker du også til at opplysningene som samles inn i dette prosjektet kan overføres til utlandet som ledd i forskningssamarbeid og publisering. Prosjektleder vil sikre at dine opplysninger blir ivaretatt på en trygg måte.

Koden som knytter deg til dine personidentifiserbare opplysninger vil ikke bli utlevert.

HVA SKJER MED PRØVER SOM BLIR TATT AV BARNET DITT?

Forskningsblodprøven som eventuelt tas av barnet ditt skal oppbevares i den generelle forskningsbiobanken "OUS Barnebiobank – barnekreft (REK nr 2016/943)", lokalisert på Oslo Universitetssykehus og med overlege Monica Cheng Munthe-Kaas som ansvarshavende.

FORSIKRING

Alle deltakere er forsikret på testdag 1 som ved andre nødvendige helseundersøkelser i henhold til pasientskadeloven og på testdag 2 ved NIHs forsøkspersonforsikring.

GODKJENNING

Prosjektet er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk, saksnr. (2018/739) og Personvernombudet ved OUS (P360 nr 18/17133)

.

Samtykke til deltakelse i PROSJEKTET

JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Som foresatte til_ (Fullt navn) samtykker vi til at hun/han kan delta i prosjektet «*Fysisk form hos barnekreftoverlevere»*

Vi tillater også at det tas blodprøve til "OUS Barnebiobank – barnekreft":

ja ☐ nei ☐ (kryss av for det som er aktuelt)

Sted og dato

Foresattes signatur

Foresattes navn med trykte bokstaver

Kontaktinformasjon:

Tlf:

Mail:

Sted og dato

Foresattes signatur

Foresattes navn med trykte bokstaver

Kontaktinformasjon:

Tlf:

Mail:

INFORMASJONSSKRIV TIL BARN UNDER 12 ÅR: KONTROLLGRUPPE

FYSISK FORM HOS BARNEKREFTOVERLEVERE

HVORFOR BLIR DU SPURT OM Å VÆRE MED?

Bakgrunnen for at vi spør om du vil delta i dette forskningsprosjektet er at vi ønsker å få vite mer om den fysiske formen til barn som har hatt kreft. For å vite om barn som har hatt kreft har utfordringer med sin fysiske form må vi sammenligne testresultatene med friske barn som ikke har fått kreftbehandling. Det kalles en kontrollgruppe. Vi lurer på om du har lyst til å delta i en slik kontrollgruppe. Hvis vi får mer kunnskap om hvilke utfordringer barn som har hatt kreft opplever kan vi sette i gang tiltak for å hjelpe dem til å være så fysisk aktive som de ønsker å være. På den måten kan vi kanskje hjelpe barn og ungdom til å få bedre fysisk form under og etter behandlingen.

HVA VIL SKJE DERSOM DU DELTAR?

Studien vil foregå på en ettermiddag og du vil gjennomføre tester ved Ullevål sykehus og på Norges idrettshøgskole. Du møter sammen med vennen/klassekameraten som har rekruttert deg og dere gjennomfører de samme testene denne ettermiddagen.

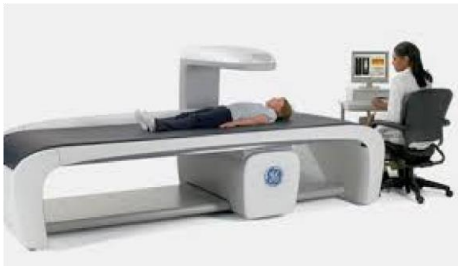
På Ullevål sykehus skal dere gjennomføre tre enkle undersøkelser av nervesystemets kontroll på muskulatur og sanseinntrykk (hvordan du bl.a. oppfatter trykk og varme mot huden). Disse undersøkelsene vil totalt ta ca. 1,5 time for dere to som testes sammen.

- Undersøkelse 1: Nevrografi: Nevrografi betyr at vi setter svak strøm i huden over ulike nerver i armene og bena for å se hvordan muskelen reagerer. Under undersøkelsen kan det gjøre litt vondt under strømstøtene, men du kan si stopp når du vil og da vil vi stoppe, til du synes det er greit å starte igjen.
- Undersøkelse 2: Termotest: Her vil vi undersøke om nerver som kjenner om det er varmt eller kaldt virker som de skal. Vi undersøker ved hjelp av en metallplate som kan varmes opp. Denne metallplaten fester vi utenpå huden. Vi undersøker i håndflaten, på fotryggen (oppå foten), på leggen og låret. Vi vil se på hvor fort du kjenner at det blir varmt. Det gjør vi ved at du trykker på en knapp når du kjenner at det blir varmere. Termotesten kan oppleves som litt ubehagelig, men dette går fort over. Du kan også si stopp når du ønsker det.
- Undersøkelse 3: Nevrologisk undersøkelse: Her vil vi undersøke nerver som sender signaler fra hjernen til musklene (motorikk), og nerver som sender signaler fra kroppen til hjernen (sanseinntrykk). Undersøkelsen skjer ved at vi spør deg noen spørsmål om hvordan du opplever at disse nervene fungerer (om du føler du har kontroll over muskler og sanseinntrykk). Vi vil også undersøke hvordan du oppfatter ulike typer berøring (å bli tatt på). Til slutt vil vi undersøke hvor sterke musklene dine er i hender og føtter, og teste refleksene dine.

Når dere er ferdige med undersøkelsene på Ullevål sykehus vil dere bli kjørt opp til Norges idrettshøgskole (NIH) der resten av de fysiske målingene gjennomføres. Kjøreturen fra Ullevål til NIH tar ca. 10 minutter. På NIH skal dere gjennomføre undersøkelsene for kondisjon (hvor god form du er i), muskelstyrke, spenst, blodvolum

(hvor mye blod du har i kroppen) og kroppssammensetning. Dere vil totalt bruke ca. 3 timer på disse undersøkelsene, og dere vil få mat og drikke underveis.

- For å se hva kroppen din består av (kroppssammensetning) vil vi gjøre en dexascan undersøkelse (minner om en vanlig røntgenundersøkelse) for å beregne muskelmasse, fettmasse og beinmasse. Deretter skal vi måle tykkelsen på én lår- og én armmuskel ved hjelp av ultralyd. Dexascan tar 15 minutter og det samme gjør ultralydundersøkelsen av bein- og armmuskel.



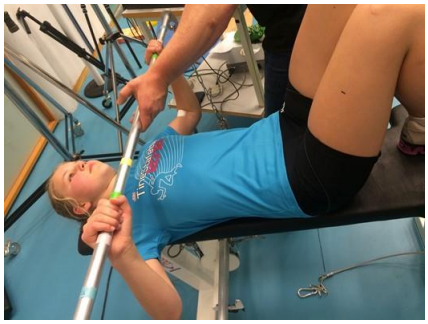
Bilde av dexascan

Bilde av ultralydundersøkelse av lår og arm

- Pustekapasiteten din vil bli målt ved at du puster på forskjellige måter inn i ett munnstykke. Lungefunksjonsmålingene gir oss et mål på hvor raskt du klarer å puste ut, hvor store lungene dine er og hvordan oksygen overføres fra lungene til blodet. Denne undersøkelsen vil ta ca. 30 min.

Bilde av utstyret som brukes til å måle pustekapasitet

- Styrke i overkroppen måles ved at du ligger på en benk og presser armene alt du orker mot en fast stang (benkpress). I tillegg måler vi håndgrepsstyrken din ved at du klemmer så hard du kan på et håndtak. Styrken i beina måles ved at du sitter og presser leggen mot en fast plate (knestrekk). På alle testene tar i alt du orker i 2-3 sekunder og gjentar dette 2-3 ganger med ett minutts pause mellom hvert forsøk. Til slutt vil vi telle hvor mange ganger du klarer å reise deg opp og sette deg ned på en stol i løpet av 1 min. Totalt tar styrketestene ca. 20 min.



Styrketest overkropp

Styrketest bein

- Kondisjonen din vil bli målt mens du går/løper på en tredemølle. Farten på tredemøllen starter rolig, og økes deretter gradvis til du ikke orker mer. Under testen har du på en maske som samler opp all luften som pustes ut slik at vi kan måle hvor mye oksygen kroppen din tar opp. Du kommer til å merke at du blir ganske sliten på slutten av denne testen (puster tungt). Undersøkelsen vil ta ca. 20 minutter, men det er kun på slutten at du blir veldig sliten. Under denne undersøkelsen vil du ha på deg utstyr som gjør at vi kan følge med på blodtykket ditt og hvordan hjertet slår.

Kondisjonstest på tredemølle

- For å kunne måle hvor mye blod du har i kroppen skal du puste i et munnstykke i et par minutter. Samtidig med testen skal det også tas en blodprøve fra armen din samt to små fingerstikk. Resultatene fra disse blodprøvene brukes til å regne ut blodvolumet ditt. Du vil få bedøvelseskrem på armen og fingrene, slik at du ikke merker når vi stikker deg.

Bilde av utstyret som brukes til å måle blodvolum

Når du er ferdig med alle undersøkelsene vil du få utdelt en aktivitetsmåler som du skal ha på deg i én uke. Du skal også fylle ut et kort spørreskjema om fysisk aktivitet og pubertet på en Ipad og det tar 10-15 minutter. Dette kan du gjøre i pausene mellom undersøkelsene.

HVA VIL SKJE DERSOM DU IKKE DELTAR

Det er frivillig å delta i prosjektet og du kan når som helst og uten å oppgi noen grunn trekke deg fra studien.

INFORMASJONSSKRIV TIL UNGDOM 12-18 ÅR: KONTROLLGRUPPE

FYSISK FORM HOS BARNEKREFTOVERLEVERE

BAKGRUNN OG HENSIKT

Bakgrunnen for at vi spør om du vil delta i dette forskningsprosjektet er at vi ønsker å få vite mer om den fysiske formen til barn og ungdom som har hatt kreft. For å vite om ungdom som har hatt kreft har utfordringer med sin fysiske form må vi sammenligne testresultatene med friske ungdommer som ikke har fått kreftbehandling. Det kalles en kontrollgruppe. Vi lurer på om du har lyst til å delta i en slik kontrollgruppe. Hvis vi får mer kunnskap om hvilke utfordringer ungdom som har hatt kreft opplever kan vi sette i gang tiltak for å hjelpe dem til å være så fysisk aktive som de ønsker å være. På den måten kan vi kanskje hjelpe barn og ungdom til å få bedre fysisk form under og etter behandlingen.

HVA INNEBÆRER STUDIEN?

Studien vil foregå på en ettermiddag og du vil gjennomføre tester ved Ullevål sykehus og på Norges idrettshøgskole. Du møter sammen med vennen/klassekameraten som har rekruttert deg og dere gjennomfører de samme testene denne ettermiddagen.

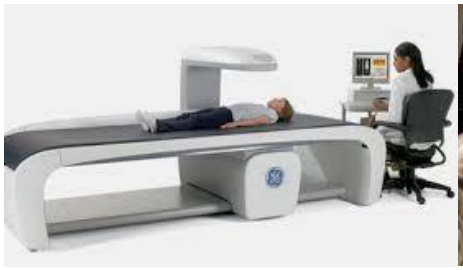
Én uke før testdagen vil du få tilsendt en aktivitetsmåler som skal bæres i én uke. På selve testdagen leverer du inn aktivitetsmåleren på Norges idrettshøgskole.

På Ullevål sykehus skal dere gjennomføre tre enkle undersøkelser av nervesystemets kontroll på muskulatur og sanseinntrykk (hvordan du bl.a. oppfatter trykk og varme mot huden). Disse undersøkelsene vil totalt ta ca. 1 time for dere to som testes sammen.

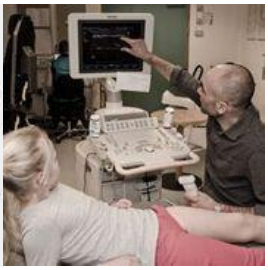
- Undersøkelse 1: Nevrografi: Nevrografi betyr at vi setter svak strøm i huden over ulike nerver i armene og bena for å se hvordan muskelen reagerer. Under undersøkelsen kan det gjøre litt vondt under strømstøtene, men du kan si stopp når du vil og da vil vi stoppe, til du synes det er greit å starte igjen.
- Undersøkelse 2: Termotest: Her vil vi undersøke om nerver som kjenner om det er varmt eller kaldt virker som de skal. Vi undersøker ved hjelp av en metallplate som kan varmes opp. Denne metallplaten fester vi utenpå huden. Vi undersøker i håndflaten, på fotryggen (oppå foten), på leggen og låret. Vi vil se på hvor fort du kjenner at det blir varmt. Det gjør vi ved at du trykker på en knapp når du kjenner at det blir varmere. Termotesten kan oppleves som litt ubehagelig, men dette går fort over. Du kan også si stopp når du ønsker det.
- Undersøkelse 3: Nevrologisk undersøkelse: Her vil vi undersøke nerver som sender signaler fra hjernen til musklene (motorikk), og nerver som sender signaler fra kroppen til hjernen (sanseinntrykk). Undersøkelsen skjer ved at vi spør deg noen spørsmål om hvordan du opplever at disse nervene fungerer (om du føler du har kontroll over muskler og sanseinntrykk). Vi vil også undersøke hvordan du oppfatter ulike typer berøring (å bli tatt på). Til slutt vil vi undersøke hvor sterke musklene dine er i hender og føtter, og teste refleksene dine.

Når dere er ferdige med undersøkelsen på Ullevål sykehus vil dere bli kjørt opp til Norges idrettshøgskole (NIH) der de fysiske undersøkelsene skal gjennomføres. Kjøreturen fra Ullevål til NIH tar ca. 10 minutter. På NIH skal dere gjennomfører målinger for kondisjon (det maksimale oksygenopptaket), muskelstyrke, spenst, blodvolum og kroppssammensetning. Undersøkelsene vil totalt ta ca. 3 timer, og dere vil få mat og drikke underveis.

- For å se hva kroppen din består av (kroppssammensetning) vil vi gjøre en dexascan undersøkelse (minner om en vanlig røntgenundersøkelse) for å beregne muskelmasse, fettmasse og beinmasse. Dessuten skal vi måle tykkelsen på én lår- og én armmuskel ved hjelp av ultralyd. Dexascan tar 10 minutter og det samme gjør ultralydundersøkelsen av bein- og armmuskel.



Bilde av dexascan

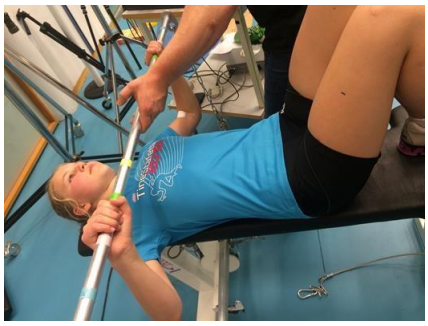


Bilde av ultralydundersøkelse av lår og arm

- Lungefunksjon vil bli målt ved at du du puster på forskjellige måter inn i ett munnstykke. Lungefunksjonsmålingene gir oss et mål på hvor raskt du klarer å puste ut, hvor store lungene dine er og hvordan oksygen overføres fra lungene til blodet. Denne undersøkelsen vil ta ca. 30 min.

Bilde av utstyret som brukes til å måle lungefunksjon

- Styrke i overkroppen måles ved at du ligger på en benk og presser armene alt du orker mot en fast stang (benkpress). I tillegg måler vi håndgrepsstyrken din ved at du klemmer så hard du kan på et håndtak. Styrken i beina måles ved at du sitter og presser leggen mot en fast plate (knestrekk). På alle testene tar i alt du orker i 2-3 sekunder og gjentar dette 2-3 ganger med ett minutts pause mellom hvert forsøk. Til slutt vil vi telle hvor mange ganger du klarer å reise deg opp og sette deg ned på en stol i løpet av 1 min. Totalt tar styrketestene ca. 20 min.



Styrketest overkropp

Styrketest bein

- Kondisjonen din vil bli målt mens du går/løper på en tredemølle. Farten på tredemøllen starter rolig, og økes deretter gradvis til du ikke orker mer. Under testen har du på en maske som samler opp all luften som pustes ut slik at vi kan måle hvor mye oksygen kroppen din tar opp. Du kommer merke at du blir ganske sliten på slutten av denne testen (puster tungt). Undersøkelsen vil ta ca. 20 minutter, men det er kun på slutten at du blir veldig sliten. Under denne undersøkelsen vil du ha på deg utstyr som gjør at vi kan følge med på blodtykket ditt og hvordan hjertet slår underveis.

Kondisjonstest på tredemølle

- For å kunne måle hvor mye blod du har i kroppen skal du puste i et munnstykke i et par minutter. Samtidig med testen skal det også tas en blodprøve fra armen din samt to små fingerstikk. Resultatene fra blodprøvene brukes til å regne ut blodvolumet ditt. Du vil få bedøvelseskrem på armen og fingrene, slik at du ikke merker når vi stikker deg. Fra blodprøven vil vi også måle tradisjonelle blodfettstoffer (kolesterol).

Bilde av utstyret som brukes til å måle blodvolum

Når du er ferdig med alle undersøkelsene vil du få utdelt en aktivitetsmåler som du skal ha på deg i én uke. Du skal også fylle ut et kort spørreskjema om fysisk aktivitet og pubertet på en IPad og det tar 10-15 minutter. Dette kan du gjøre i pausene mellom undersøkelsene.

MULIGE FORDELER OG ULEMPER

Ved å være med på denne undersøkelsen vil du lære litt om kroppen din og hvordan forskning foregår. Under den nevrologiske undersøkelsen settes det svak strøm i huden og disse strømstøtene kan gjøre litt vondt. Termotesten innebærer varmestimulering som kan oppleves som lett til moderat, men kortvarig ubehag. I forbindelse med måling av blodvolum må vi ta en blodprøve fra en armvene. Vi bedøver huden der vi skal ta blodprøven, men det vil likevel gjøre litt vondt. Ingen øvrige undersøkelser er forbundet med smerte. Måling av maksimalt oksygenopptak ved løp på tredemølle kan oppleves som slitsomt, og det kreves at du løper til du blir ganske sliten.

HVA SKJER MED PRØVENE OG INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til opplysninger gjennom en navneliste.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg vil bli anonymisert eller slettet senest fem år etter prosjektslutt.

DELTAKELSE

Det er frivillig å delta i prosjektet. Du kan når som helst og uten å oppgi noen grunn trekke deg fra studien. Dette vil ikke få konsekvenser for videre behandling. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte PostDoc Elisabeth Edvardsen (tlf: 23262391, epost: elisabeth.edvardsen@nih.no).

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET FOR DITT BARN - KONTROLLGRUPPE

FYSISK FORM HOS BARNEKREFTOVERLEVERE

Dette er et spørsmål til deg som foresatt om ditt barn kan delta i et forskningsprosjekt på fysisk form etter barnekreftbehandling. Din sønn/datter har en venn som tidligere har blitt behandlet for kreft og som ønsker å invitere med din sønn/datter inn i forskningsprosjektet. I studien på barnekreftoverlevere ønsker vi å sammenlikne funnene hos de som har gjennomgått kreftbehandling med funnene hos jevnaldrende av samme kjønn fra samme miljø som ikke har gjennomgått kreftbehandling. Derfor får dere denne forespørselen. Hvis dere samtykker til at deres barn kan delta i denne studien vil deres barn være en av kontrollene og vil møte til testen sammen med hans/hennes venn som er frisk etter kreftbehandling.

Barnekreftbehandling kan påvirke kroppen på mange måter. Under aktiv behandling reduseres vanligvis den fysiske formen, og det kan ta tid før man henter seg inn igjen etter behandlingsslutt. Redusert aktivitetsnivå og seineffekter etter behandling kan påvirke barnekreftoverlevernes fysiske form og helse mange år etter behandlingsslutt. Det er disse utfordringene knyttet til fysisk form og fysisk aktivitet vi ønsker å undersøke i denne studien for eventuelt å sette inn tiltak som bedrer formen for ungdomsgruppen på kort og lang sikt. For å vite om den fysiske formen er dårligere hos barnekreftoverlevere enn hos den generelle befolkningen, og for å få mer kunnskap om hva som er utfordringene for barnekreftoverleverne, er vi avhengig av kunne sammenligne dem med friske jevnaldrende kontroller.

HVA INNEBÆRER PROSJEKTET?

Alle testene vil bli gjennomført på en ettermiddag. Første del av testene vil foregå på Nevrofysiologisk laboratorium på Ullevål sykehus og andre del på Norges idrettshøgskole.

På Nevrofysiologisk laboratorium på Ullevål sykehus gjennomføres tre enkle undersøkelser av nervesystemets kontroll på muskulatur og sanseinntrykk (hvordan vi bl.a. oppfatter trykk og varme mot huden). Dette er standard kliniske undersøkelser, og det vil totalt ta ca. 1 time for de to barna som kommer til test samtidig.

1. Nevrografi: Formålet med undersøkelsen er å måle de tykke nervefibrene, både utoverledende (til muskler) og innoverledende (sanseinntrykk). Ved nevrografi setter vi svak strøm i huden over ulike nerver i armene og bena og registrerer effekt på muskelen ved hjelp av en elektrode festet til huden. Vi setter også strøm i huden og registrerer i huden over visse nerver. Det er ikke risiko for varige skader av denne undersøkelsen. Under undersøkelsen kan det kjennes noe smerte under strømstøtene. Metoden har vært rutineundersøkelse på pasienter i flere tiår og gjennomføres vanligvis uten problemer.
2. Termotest: Formålet med undersøkelsen er å kartlegge funksjonen til tynne nervefibre som har med temperaturoppfattelse å gjøre. Vi undersøker ved hjelp av en metallplate som kan varmes opp. Denne metallplaten fester vi utenpå huden. Vi undersøker i håndflate, fotrygg, legg og lår. Vi vil se på tersklene for oppfattelse av varme og barnet trykker selv på en knapp når det kjenner temperaturendring. Termotesten innebærer varmestimulering som kan oppleves som lett til moderat, men kortvarig ubehag.
3. Nevrologisk undersøkelse: Formålet med den nevrologiske undersøkelsen er å vurdere om pasienten har symptomer eller tegn på nedsatt funksjon i nerver som formidler signaler til muskler (motorikk), eller i nerver som leder signaler innover (sanseinntrykk), eller i nerver som tilhører det autonome

nervesystemet. Undersøkelsen skjer dels ved at det stilles noen spørsmål om vedkommende har aktuelle symptomer, dels ved at det undersøkes for respons på ulike typer berøring og for muskelstyrke i hender og føtter samt at det gjøres testing av dype senereflekser. Undersøkelsen er ikke smertefull og innebærer ikke risiko.

På Norges idrettshøgskole gjennomfører barna testene for kondisjon (det maksimale oksygenopptaket), muskelstyrke, spenst, blodvolum og kroppssammensetning. Testene vil totalt ta ca. 3 timer og barna vil få enkel servering underveis (mat og drikke).

- Kroppssammensetning for beregning av muskelmasse, fettmasse og beinmasse vil bli målt ved en dexascan (DXA) undersøkelse (minner om en vanlig røntgenundersøkelse). Dessuten skal vi måle tykkelsen på én lår- og én armmuskel ved hjelp av ultralyd.
- Styrke måles ved å ligge på en benk og presse armene mot en fast stang (isometrisk benkpress), ved å klemme så hardt man klarer mot et håndtak (håndgrepsstyrke), og ved å sitte og presse leggen mot en fast plate (isometrisk knestrekk). I tillegg vil vi telle hvor mange ganger barnet klarer å reise seg opp og ned fra en stol på 1 min.
- Det maksimale oksygenopptaket vil bli målt mens man løper på en tredemølle. Hastigheten økes gradvis til man blir ganske sliten. Under testen har man på en maske på som samler opp all luften som pustes ut slik at vi kan måle oksygenopptaket. Barna har på seg elektroder og blodtrykksmåler under denne undersøkelsen slik at vi kontinuerlig følger med på hjertefrekvens og blodtrykk.
- Måling av blodvolum skjer ved at man puster i et munnstykke forbundet med et kammer med oksygen tilsatt en liten mengde karbonmonoksid (som ofte kalles CO). Samtidig med testen skal det tas en blodprøve fra en armvene for måling av blodsammensetning. Resultatene fra denne blodprøven brukes sammen med Hb-massen til å regne ut blodvolumet.

I prosjektet vil vi innhente og registrere opplysninger om barnet ditt. Opplysningene som blir registrert er:

1. Resultater fra den nevrologiske undersøkelsen
2. Resultater fra aktivitetsmålingen
3. Resultater fra måling av kroppssammensetning
4. Resultater fra måling av muskelstyrke og spenst
5. Resultater fra måling av kondisjon (maksimalt oksygenopptak)
6. Resultater fra måling av blodvolum
7. Spørreskjema: I pausene mellom undersøkelsene vil barnet fylle ut et spørreskjema om pubertetsstatus, fysisk aktivitet, trøtthet og motivasjon for fysisk aktivitet på en Ipad.

Etter at alle undersøkelsene er gjennomført på Norges idrettshøgskole får dere utlevert en aktivitetsmåler. Den skal barnet ha på seg i én uke og aktivitetsmåleren sendes deretter i posten tilbake i ferdig frankert konvolutt.

Alle data lagres i en sikker database ved Norges idrettshøgskole (NIH).

MULIGE FORDELER OG ULEMPER

Ved å være med på denne undersøkelsen vil barna lære litt om kroppen sin og hvordan forskning foregår. Under den nevrologiske undersøkelsen settes det svak strøm i huden og disse strømstøtene kan for noen oppleves som ubehagelig. Termotesten innebærer varmestimulering som kan oppleves som lett til moderat, men kortvarig ubehag. I forbindelse med måling av blodvolum må vi ta en blodprøve fra armvene. Vi bedøver huden der vi skal ta blodprøven slik at det ikke skal gjøre vondt. Ingen øvrige undersøkelser er forbundet med smerte. Måling av maksimalt oksygenopptak ved løp på tredemølle kan oppleves som slitsomt, og det kreves at de løper til de blir ganske slitne.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker at barnet ditt skal delta, undertegner du samtykkeerklæringen på siste side. Vi trenger samtykke fra begge foreldrene. Du kan når som helst og uten å oppgi noen grunn trekke samtykket til at ditt barn skal delta i studien. Dette vil ikke få konsekvenser for ditt barn eller for barnekreftoverleveren som ditt barn testes sammen med. Dersom du trekker barnet ditt fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte PostDoc Elisabeth Edvardsen (tlf: 23262391, epost: elisabeth.edvardsen@nih.no).

HVA SKJER MED INFORMASJONEN OM BARNET DITT?

Informasjonen som registreres om barnet ditt skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter barnet til opplysninger gjennom en navneliste.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om barnet ditt blir behandlet på en sikker måte. Informasjon om barnet ditt vil bli anonymisert eller slettet senest fem år etter prosjektslutt.

Etter ny personopplysningslov har behandlingsansvarlig Norges idrettshøgskole og prosjektleder Truls Raastad et selvstendig ansvar for å sikre at behandlingen av ditt barns opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6a og 9a. Du har rett til å klage på behandlingen av deres opplysninger til Datatilsynet.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet kan du kontakte prosjektleder Truls Raastad, tlf.: 23262328, mail: truls.raastad@nih.no. Du kan ta kontakt med institusjonens personvernombud dersom du har spørsmål om behandlingen av ditt barns personopplysninger i prosjektet, Karine Justad, e-post: karine.justad@nih.no, tlf. 232 62 089.