PHYSICAL DETERMINANTS OF PHYSICAL ACTIVITY IN CHILDREN WHO HAVE COMPLETED TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKEMIA

by

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Abstract

INTRODUCTION: Physical activity (PA) levels in children who have completed treatment for acute lymphoblastic leukemia (ALL) have been shown to be lower than their healthy peers. Obesity and related health concerns have been recognized as long-term side-effect of cancer treatment. Motor performance and physical function have been shown to be lower in these children compared with children who have not had a cancer diagnosis. Whether or not these two physical factors are related to PA levels in these children is unknown. PURPOSE: To determine if motor performance and physical function are associated with PA in children who have completed treatment for ALL. METHODS: PA was measured using the Physical Activity Questionnaire for Older Children (PAQ-C); motor performance was measured using the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition, Short Form (BOT-2 SF); and physical function was measured using the Six-Minute Walk Test (6MWT). RESULTS: Thirteen participants were recruited. PAQ-C scores were not related to standardized scores from the BOT-2 SF (Spearman’s rho, $r_s = 0.282$, $p = 0.35$) and 6-minute walk distance (6MWD) ($r_s = -0.429$, $p = 0.14$) and 6MWD Standard Deviation Score (SDS) ($r_s = -0.094$, $p = 0.76$). Only 1/13 participants performed below average in the BOT-2 SF, and 11/13 participants walked shorter distances compared with published data from healthy children in the 6MWT (mean 6MWD SDS: -1.62). Body mass index SDS were significantly associated with measured 6MWD ($r_s = 0.602$, $p = 0.03$) and 6MWD SDS ($r_s = -0.691$ $p = 0.01$). CONCLUSION: PA was not associated with motor performance or physical function. Physical function was poorer compared with healthy children in 11/13 participants. Healthcare professionals can focus on improving physical function and improving weight management to help reduce risk of obesity and associated health consequences in children who have completed treatment for ALL. Future research should
include a larger sample size and include psychosocial factors, such as self-efficacy and parental influence, in exploring factors related to PA childhood ALL survivors.
Preface

This thesis contains the work of a research study conducted by the candidate, Stanley H. Hung, under the supervision of Dr. Kristin L. Campbell with guidance from Anne Rankin, and Drs. Mark Beauchamp and Naznin Virji-Babul from the University of British Columbia, Vancouver, as well as Angela Pretula, Marion Nelson, and Drs. Sheila Pritchard and Christopher Fryer from the British Columbia Children’s Hospital. The study design, data collection and analysis, and writing of the manuscript were primarily the work of the candidate.

Sections of this thesis will be submitted for publication as manuscript in peer reviewed journals.

Ethical approval for this research study was provided by the Children’s and Women’s Research Ethics Board (H13 - 01823).
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<td>6MWD</td>
<td>Six Minute Walk Distance</td>
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<td>6MWT</td>
<td>Six Minute Walk Test</td>
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<td>ALL</td>
<td>Acute Lymphoblastic Leukemia</td>
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<td>ATS</td>
<td>American Thoracic Society</td>
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<td>BCCH</td>
<td>British Columbia Children’s Hospital</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BOT-2 SF</td>
<td>Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition, Short Form</td>
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<tr>
<td>BOTMP</td>
<td>Bruininks-Oseretsky Test of Motor Proficiency, 1st Edition</td>
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<tr>
<td>CF</td>
<td>Cognitive Fatigue</td>
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<td>DMT</td>
<td>Deutscher Motorik-Test</td>
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<td>GF</td>
<td>General Fatigue</td>
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<tr>
<td>GLTEQ</td>
<td>Godin Leisure time Exercise Questionnaire</td>
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<td>HW</td>
<td>Healthy Weight</td>
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<tr>
<td>LTFU</td>
<td>Long-Term Follow-Up clinic</td>
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<td>MOT</td>
<td>Motoriktest</td>
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<td>OWO</td>
<td>Overweight and Obese</td>
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<td>PAQ-C</td>
<td>Physical Activity Questionnaire for Older Children</td>
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<td>SDS</td>
<td>Standard Deviation Score</td>
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<td>SRF</td>
<td>Sleep/Rest Fatigue</td>
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<td>U</td>
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Dedication

I would like to dedicate this thesis to my parents, Kenny and Ivy Hung, my older brother, Delbert Hung, and to the rest of my dearest family. Without you, my wonderful experience as a graduate student at the University of British Columbia would not have been possible. Thank you for your emotional support and inspiration throughout my life.
Chapter 1: Literature Review

1.1 Introduction

Acute lymphoblastic leukemia (ALL) is currently the most common childhood malignancy accounting for more than 25% of all childhood cancers\(^1\). With recent advances in treatment approaches, children diagnosed with ALL have significantly improved 5-year survival rates, which are currently above 85% in developed countries\(^2\), and 94% in Canada\(^3\). As a result, research has now become more focused on treatment side effects. Potential late effects of therapeutic interventions for childhood cancers of any diagnosis include altered cardiovascular, pulmonary, liver, renal, bladder, endocrine, musculoskeletal, neurocognitive and nervous system function\(^4\). Specific to children with ALL, impaired physical performance measures have been documented in this population, including lower peak oxygen consumption\(^5,6\), reduced motor performance and physical function\(^7\), reduced quality of life, and reduced self-perception of adequacy and predilection for physical activity\(^8\).

Physical activity (PA) levels in children who are undergoing treatment or who have completed treatment for ALL, as well as adult long-term survivors of ALL, have been shown to be lower compared to their healthy counterparts\(^9\). However, the factors influencing PA levels are unclear\(^9,10\). Both physical and psychosocial factors have been acknowledged as potential mechanisms for lowered PA levels\(^11\). Few studies have investigated the physical factors related to PA levels in children who have completed treatment for ALL\(^7,12-14\). The importance of understanding PA patterns in this population is due to the well-established benefits of PA in healthy children\(^15\). A higher risk of obesity, diabetes mellitus, and cardiovascular disease are now recognized as potential late effects of treatment for ALL in children\(^16,17\), which may be linked to the lower levels of PA in this population. This study aims to investigate two physical
factors potentially affecting PA levels in children who have completed treatment for ALL, specifically motor performance and physical function.

1.2 ALL Biology and Epidemiology

According to the Canadian Cancer Society in 2014 for children diagnoses between the age of 0 – 14, leukemia accounted for 32% of the 4,600 new cases of childhood cancers reported from 2006 – 2010, 26% of the 640 deaths reported from 2005 – 2009, and had a 5-year observed survival proportion of 91% from 2004 – 2008. The remainder of this thesis will refer to patients who have completed primary treatment for ALL without recurrence as cancer survivors.

ALL is characterized by an abnormal accumulation of malignant immature white blood cells (lymphoblast) in the bone marrow. These abnormal lymphoblasts fail to differentiate into mature cells, preventing healthy development of healthy erythrocytes, lymphocytes and platelets, and ultimately leading to anemia and susceptibility to infection. In general, ALL can be classified as B-Lineage and T-Lineage. B-Lineage is a malignancy involving lymphoblasts committed to the B-cell lineage, while T-Lineage refers to lymphoblasts committed to the T-cell lineage. B-lineage ALL is generally associated with 85% survival, while T-lineage ALL is generally considered the more aggressive, high-risk disease but accounts for 15% of ALL cases in children. Subtypes of ALL can be further classified based on genetic characteristics to help profile a child’s susceptibility to developing ALL, their prognosis and response to treatment, disease severity, and their likelihood of relapse or recurrence. These genetic profiles are often related to a patient’s abnormal immunological response to infection. The understanding of these genetic profiles is evolving and remains highly debated. However, this has led to the development of two hypotheses in explaining the etiology of ALL.
The first hypothesis is the Kinlen Population Mixing Hypothesis\textsuperscript{22} and suggests leukemia is a result of an influx in large numbers of people moving and mixing to create rare incidences of abnormal responses to specific viral infections. The second hypothesis is the Greaves Delayed Infection Hypothesis\textsuperscript{23}, stating that children who have had an under stimulated immune system during childhood development will display an over-response to common infections later in childhood, and subsequently induce leukemia in children with genetic mutations making them susceptible to leukemia. Epidemiological evidence has also suggested that electromagnetic radiation may be related to a slightly increased risk of ALL, though the reliability of this data remains uncertain\textsuperscript{24}.

Upon diagnosis, ALL patients are typically started on a two to two-and-a-half year chemotherapy treatment plan comprising of four therapy phases: induction of remission, consolidation, delayed intensification, and maintenance therapy\textsuperscript{20}. Induction of remission therapy phase is generally four to six weeks with the goal of eliminating all initial leukemic cells and restoring normal blood cell production, allowing the patient to be in a remission, cancer-free, status. Chemotherapy during this phase of treatment generally includes using glucocorticoids, vincristine, and asparaginase, and potentially involving the use of anthracyclines. The consolidation and delayed intensification therapy phases together are approximately 20 – 30 weeks of chemotherapy to help eliminate residual leukemic cells, and generally includes high doses of methotrexate and mercaptopurine with pulses of vincristine and glucocorticoids. Finally, the maintenance therapy phase lasts approximately two or more years and aims to keep the patient in remission and prevent relapse. This phase mainly uses mercaptopurine, methotrexate, with or without pulse of vincristine and dexamethasone. Each of the drugs used during the course of chemotherapy are associated with potential adverse late effects.
1.2.1 Physical Late Effects of Chemotherapy

With improvements in survival rate, research has increasingly been focused on the adverse effects of chemotherapy in those who have been diagnosed with childhood ALL and have completed primary adjuvant treatment. Anthracyclines, glucocorticoids, and vincristine are common agents used to treat children with ALL, and each has been reported to have adverse late effects. Exposure to anthracyclines during ALL treatment has been associated with cardiotoxic effects, which can potentially result in cardiomyopathy and congestive heart failure, both of which may be irreversible, and manifests as reduced left ventricular mass and thickness, and depressed left ventricular contractility in long-term survivors of childhood cancers. Corticosteroids, such as dexamethasone, have been associated chronic fatigue and osteonecrosis, the general term used to describe cell death of segments of cortical bone tissue. Vincristine, an alkaloid agent used in chemotherapy regimens to treat many types of cancers, has been associated with peripheral neuropathy in children treated for ALL.

1.3 Physical Effects of Treatment on ALL Patients

San Juan et al. have reported on the potential late effects of therapeutic interventions for childhood cancers of any diagnosis, specifically cardiovascular, pulmonary, liver, renal, bladder, endocrine, musculoskeletal, neurocognitive and nervous system function. Specific to ALL, observational studies investigating the post-treatment effects for children with ALL have found lower peak oxygen consumption compared to controls, reduced muscle strength and mobility as measured by the Timed Up and Go and 2-minute walk test; lower self-perception of adequacy and predilection for PA than healthy controls; and lower overall quality of life compared with healthy controls. Since the outcome measures of the current thesis focuses on
motor performance and physical function in childhood ALL survivors, we will focus on reviewing studies who have investigated these outcomes.

1.3.1 Motor Performance

Previous studies investigating the motor performance in childhood cancer patients have found mixed results. Green et al.\textsuperscript{32} conducted a systematic review and found 28 peer-reviewed studies investigating motor performance in children diagnosed with ALL, both during and following treatment. Articles were included if studies assessed motor performance in children who were 0 – 18 years old, have been or were being treated with chemotherapy without radiation, used standardized motor measurement tools, and included a sample of greater than 10 participants who were diagnosed with ALL. Motor performance was categorized as gross and fine motor performance, where gross motor performance included measurement tools testing muscle strength, maintaining balance, ball skills, and agility, and fine motor performance included measurement tools testing manual dexterity, handwriting, and drawing skills.

Their review included seven studies that assessed gross motor performance; two during treatment\textsuperscript{33,34}, four studies after treatment \textsuperscript{29,35-37}, and one both before and after treatment\textsuperscript{38}. Three studies were longitudinal\textsuperscript{33,34,38} and four were cross-sectional\textsuperscript{29,35-37}. The age for the children in these studies ranged between 5.3 – 15.5 years and the time after treatment range of 0 – 7.4 years. The most frequently used motor performance measurement tool was the Movement Assessment Battery in Children (MABC), which was used by five studies. One study used the Bruininks-Oseretsky Test of Motor Performance, 2\textsuperscript{nd} Edition (BOT-2).

Specific to gross motor performance, two studies found gross motor impairments in children at diagnosis\textsuperscript{34,38}. In the four off-treatment cross-sectional studies, gross or general motor
impairment was noted in 25 – 54% of patients using the MABC\textsuperscript{29,35,36}, while one study\textsuperscript{37} found 2/37 patients performed below average on the BOT-2.

Fine motor skills were assessed by 15 studies. The common measurement tools were the Purdue Pegboard task (five studies), the MABC (four studies), Finger Tapping task (four studies), and writing tasks (two studies). Participants were children within the age range of 3.1 – 17.7 years at the time of assessment and 0 – 10 years since the time of treatment. Six studies examined fine motor skills after treatment\textsuperscript{29,35,39-42}, five during treatment\textsuperscript{33,34,42-44}, and four both before and after\textsuperscript{45-48}. In studies during treatment, two studies found reduced manual dexterity scores\textsuperscript{34,46}, and one study showed greater handwriting difficulties in terms of slower drawing speed, longer pause duration, and greater pen pressure compared with controls\textsuperscript{34}. Inconsistent data for fine motor skills after diagnosis were found in five studies; three studies showed increasing fine motor performance issues after treatment\textsuperscript{34,45,47}; and two studies\textsuperscript{39,40} showed no significant difference in fine motor skills (dexterity scores and writing speed and quality) approximately four years after treatment compared to controls.

Recent studies in children with ALL that were not included in the systematic review by Green et al.\textsuperscript{32} reported similar findings in motor performance. Hartman et al.\textsuperscript{7} studied motor performance using the MABC-2 in 34 children treated for ALL (average age of 12.3 years) and measured motor performance at the end of treatment and at a follow-up session at least five years after treatment (mean of 5.2 years). Twenty-six children completed the motor performance tests at both time points; 58% of children achieved normal scores for both time points; 38% were “at risk for impairment” at end of treatment, but achieved normal scores at follow-up; and 4% (one participant) were “at risk” at both time points.
Leone et al.\textsuperscript{49} assessed the gross motor skills of 20 childhood survivors of ALL between the ages of 9 – 11 (mean age of 10.6) and who have been off treatment for at least one year. The authors used the University of Quebec in Chicoutimi and University of Quebec in Montreal (UQAC-UQAM) norm-referenced, gross motor skills test battery, and found ALL patients had poorer performance than healthy controls in ten of the 11 motor tasks with 48.2\% of ALL patients performing below the 15\textsuperscript{th} percentile.

De Luca et al.\textsuperscript{50} studied gross and fine motor skills in 37 ALL patients who had completed treatment within the past five years (mean age 100.0 months) using the MABC-2 and the BOT-2 Short Form (BOT-2 SF). No statistically significant difference between patient and population norm scores was found with either motor tests. The children were also stratified into three groups based on their time since treatment completion, and time off treatment did not affect motor performance using either measurement tool. However, they found that 16.2\% of patients within the sample were considered impaired using the BOT-2, which was comparable to the 17\% of patients with impaired performance observed in the normal population.

Beulertz et al.\textsuperscript{51} used specific deficit analysis to study the motor performance and quality of life of 26 children (average age of 9.1 years) of mixed pediatric cancer diagnoses (n = 11 were ALL) at different stages during and after treatment. The study used two German standardized motor test batteries for children ages 4 – 6 years and 6 – 18 years called the Motoriktest (MOT) 4 – 6 and Deutscher Motorik-Test (DMT) 6 –18, respectively. The authors found more than 27\% of patients performed below the average norm-reference scores. Specifically for each age group, children ages 4 – 6 years old did not have a lower global motor performance, but had specific deficits in motor speed and control. In contrast, children ages 6 – 17 years had a lower global motor score, with 34\% scoring below the average norm-reference, and had specific deficits in
endurance, strength, flexibility, and coordination under pressure. ALL patients were not reported to have significant differences in motor performance than other cancer diagnoses, nor did patients with and without vincristine treatment perform differently.

1.3.2 Physical Function

The Six-Minute Walk Test (6MWT) is an objective measure representing submaximal exercise functional capacity and cardiopulmonary fitness\(^{52}\). For the purpose of the current study, submaximal exercise functional capacity will now be referred to as physical function. In addition to the 6MWT, a recent Cochrane Review done by Braam et al.\(^{53}\), which included randomized and clinical controlled trials of exercise training interventions for people who were within the first five years of diagnosis of ALL, physical function was also measured using the 9-minute run-walk test, timed up-and-down stairs test, and 20-m shuttle run test.

Four recent studies investigated physical function in childhood cancer survivors using the 6MWT. Hartman et al.\(^{7}\) studied physical function five years after treatment using the 6MWT, and all 34 participants performed significantly lower than healthy children of similar age and height by a mean of -2.05 standard deviation score. Hoffman et al.\(^{13}\) studied physical function using the 6MWT, timed up-and-go (TUG), hand grip strength, lower-extremity strength in 183 childhood cancer survivors of mixed cancer diagnoses (average age 13.5 years) with an average of 9.3 years post-treatment and 147 sibling as controls. The mean 6-minute walk distance (6MWD) for children of mixed cancer diagnoses was 567.8 m, and children with a leukemia or lymphoma diagnosis walked a mean 6MWD of 572.2 m. Both mixed cancer and leukemia or lymphoma patient groups walked a shorter distance compared to their siblings (594.1 m), but this relationship was only significant with the entire sample of children of mixed cancer diagnoses. Hooke et al.\(^{54}\) studied physical function, using the TUG and 6MWT in 16 children (6 – 12 years)
and 14 adolescents (13 – 17 years) receiving chemotherapy for childhood cancers. Although not statistically significant, 6MWD improved from the first (359.05 m) to the third (406.4 m) cycle of treatment for children, but not for adolescents. Children with ALL had greater improvements than those with lymphoma and solid tumour groups. Fatigue, measured using the Childhood Fatigue Scale, was also found to be negatively associated with 6MWD. Hooke et al.\textsuperscript{55} studied physical function using the 6MWT in 29 children ages 6 – 17 years old receiving treatment for cancer of mixed diagnosis, and found no change in the mean distance walked from the first (414.71 m) to third (447.23 m) cycle of chemotherapy, but 93% of patients performed one or more standard deviations below the norm for the 6MWT.

1.4 PA in ALL Patients and Survivors

PA levels of children with ALL have been well studied. Winter et al.\textsuperscript{9} conducted a systematic review on PA levels in children of any cancer diagnosis, both during and after treatment. The review included 12 studies investigating PA levels in childhood leukemia patients. All studies were cross-sectional, and three studies involving PA during treatment\textsuperscript{10,56,57}, six studies investigating PA during the first ten years of treatment completion\textsuperscript{58-63}, and three studies involving long-term adult survivors of childhood cancer\textsuperscript{64-66}. Four studies included child and adolescent cancer survivors with any leukemia diagnosis, with the majority of subjects being ALL, and reported lower levels of PA compared with healthy controls using accelerometers\textsuperscript{62}, heart rate monitors\textsuperscript{59}, or self-report questionnaires\textsuperscript{61,63}. These studies included ALL survivors who were between 1.5 years after treatment to 23.1 years after diagnosis with a mean age between 4.0 – 14.6 years old.

Three studies reported PA levels during different phases of treatment. One study was conducted during induction and consolation treatment\textsuperscript{56} and the other was conducted during
maintenance, and found significantly reduced time spent in moderate-to-high levels of PA using accelerometers. One study used doubly labeled water, a gold standard measure of total energy expenditure during a period of time, found lower energy expenditure from PA compared with controls in children with an average of 2.9 years after diagnosis for ALL.

A number of recent studies not included in the review by Winter et al. focused on the effect of treatment on PA levels, and have found similar trends in PA levels for children with ALL to the review. Fuemmeler et al. studied the relationship between PA, diet, and body composition changes in children during the first year of treatment for childhood ALL and lymphoma (n = 15) compared to age, race, and sex-matched healthy controls (n = 15; average age not reported). The average age of cancer patients was 10.3 years at study enrolment and the majority (n = 12) of children had a diagnosis of ALL. The study measured PA using accelerometers. Children with cancer performed significantly less moderate-to-vigorous PA at six month and 12 month after starting treatment compared with healthy controls (p < 0.01).

Götte et al. used self-report questionnaires to study PA in 130 children and adolescents (average age of 12.2 years) before and during cancer treatment, with the majority of children being children with leukemia (n = 44). Using reference values from the PA questionnaire from the German Health Interview and Examination Survey for Children and Adolescents, the study found patients reported normal PA level before diagnosis, but at an average of three months after diagnosis patients reported a 91% reduction in minutes/week of physical exercise (baseline, 209 minutes/week vs. during treatment, 18 minutes/week; p < 0.001). Patients also reported being less interested in sports during treatment, and a lower percentage of children met PA recommendations and did not walk as much during in-patient stays.
Orsey et al.\textsuperscript{70} studied PA and sleep using accelerometers in 23 children and 13 adolescents (average age not published) who were actively receiving chemotherapy and/or radiation, and found they were less physically active and had poorer sleep quality than healthy children. Tan et al.\textsuperscript{71} used accelerometers to measure PA levels in 38 healthy children and compared them with 38 children with ALL undergoing induction or consolidation chemotherapy, and found leukemia patients to have lower PA levels compared to healthy children (p < 0.01).

Studies investigating PA levels in children during treatment for ALL have consistently shown reduced PA compared with healthy controls. It has been suggested that these reduced PA levels during treatment remain the same after treatment completion\textsuperscript{17}. However, well-defined reasons for reduced levels of PA in children receiving treatment or children who have completed treatment for ALL remain unclear\textsuperscript{9,10}.

\subsection*{1.4.1 Potential Reasons for Reduced PA in ALL Patients and Survivors}

The reason for reduced levels of PA in childhood cancer patients and survivors has been discussed in the literature. Götte et al.\textsuperscript{69} suggested that the lower PA levels during treatment were a result of permanent restriction by treatment-related equipment, such as the infusion stand, wheel chairs, or forearm crutches. Winter et al.\textsuperscript{56}, with similar reasoning, suggested these significantly reduced PA levels of patients undergoing treatment were due to patients being connected to medical devices, which inherently restricted them to the wards and reduced their mobility. The opinion of Tan et al.\textsuperscript{71} as to why patients undergoing treatment were less active was because patients rarely leave their beds during their stay in the ward due to fatigue or experience unpleasant treatment side effects, and also spend a large amount of time in bed resting, watching television, or playing computer games for leisure entertainment. Accelerometer data from Tan et al.\textsuperscript{71} also found patients undergoing consolidation therapy to be more physically
active than patients undergoing induction therapy, and reasoned that consolidation may be a less intense therapy phase compared with induction therapy. Tan et al.\textsuperscript{71} also suggested the difference in PA levels by phase of treatment may be that by the time of consolidation therapy, patients have become better at coping with the disease and treatment over time, allowing them to better manage the side effects and to spend less time in bed, or that patients in consolidation may have familiarized themselves with the hospital environment and medical devices throughout the course of receiving treatment, making them less afraid to move around within the ward\textsuperscript{71}. Aznar et al.\textsuperscript{10} found patients in maintenance therapy had comparable PA levels to healthy controls because maintenance therapy patients were treated as outpatients, and therefore were not confined to inpatient ward settings, and reintegrated back into homes and schools with exposure to common forms of leisure activity. Based on these findings, experts have hypothesized that patients with an inactive lifestyle during treatment may allow inactivity to persist throughout maintenance therapy or after treatment completion; therefore these time points have been suggested as suitable times to reintroduce habitual PA in these children\textsuperscript{9,10}.

1.5 Impact of Time During Treatment and Time After Treatment

Previous longitudinal studies have investigated changes in motor performance, physical function, and PA during the course of treatment and/or after treatment. Vainionpaa\textsuperscript{72} evaluated motor abilities in childhood ALL patients at diagnosis and four time points during treatment, and found impairments in fine and gross motor performance in 18\% and 30\% of participants, respectively after 2 – 3 years of therapy compared to diagnosis. Hockenberry et al.\textsuperscript{46} longitudinally assessed fine motor performance within six months of diagnosis, and one and two years after diagnosis, and found mean visual-motor integration scores for low and high-risk ALL children to decrease from within six months of diagnosis to one and two years follow-up.
Hartman et al.\textsuperscript{38} conducted a longitudinal study following ALL patients for two years from diagnosis, and found an improvement in motor performance from diagnosis to end of treatment based on mean standard deviation scores. Hartman et al.\textsuperscript{7} assessed motor performance at two time points, end of treatment and 5-year follow-up, and found 38\% of participants who had been “at risk for impairment” at the end of treatment improved to normal scores at follow-up.

Two longitudinal studies assessed physical function, specifically using the 6MWT, during treatment at multiple time-points\textsuperscript{54,55}. One of the studies\textsuperscript{55} hypothesized physical function would decrease with treatment and that the related adverse side-effects would be exacerbated over time. Instead, the study found that distance walked on the 6MWT did not change significantly from the first to third cycle of chemotherapy. The other study\textsuperscript{54}, in contrast, found children ages 6 – 12 years old improved in 6MWT performance from the first to third cycle of chemotherapy, but did not see any change in adolescents ages 13 – 18 years old.

Three studies measured PA longitudinally during treatment\textsuperscript{68,69,71}, but only two had baseline measures, with one having accelerometer data of PA within 5 months of diagnosis\textsuperscript{68}, and the other having self-report retrospective PA of a typical week prior to diagnosis\textsuperscript{69}. Tan et al.\textsuperscript{71} used accelerometers and found patients undergoing consolidation therapy had higher levels of PA compared to patients in induction therapy. Götte et al.\textsuperscript{69} found a significant reduction in self-report daily PA and minutes of exercise per week from before treatment to three months after treatment. Fuemmeler et al.\textsuperscript{68} used accelerometers and found patients had greater levels of moderate-to-vigorous PA from within five months after diagnosis to 12 months after diagnosis (while still on treatment), but ALL patients were still less physically active compared with healthy controls.
1.6 The Relationship between Late Effects and PA

While research investigating the factors influencing PA levels in ALL survivors is beginning to emerge, the factors influencing PA levels remain unclear\(^9,10\). The two suggested points of view are physiological and socio-environmental factors\(^11\). Socio-environmental factors will be referred to as psychosocial factors in this document. As discussed above, the physiological factors refer to the adverse physical outcomes of cancer and cancer treatment that reduce the child’s physical capacity to perform PA. Psychosocial factors refer to lower self-reported comfort with emotional and physical symptoms and limitations, and lower resilience with positive activities promoting health\(^10\). The result of this is suggested to be a “spectrum of disuse” encouraged by parents and physicians to protect the child’s health after a life threatening disease\(^11\); and overprotection by parents potentially changing the child’s perception of their actual capacity for PA, and thus creating a fear of overexertion and low self-efficacy\(^10\).

1.6.1 Physiological Factors Associated with PA in ALL Survivors

Few studies have directly investigated the physiological factors associated with PA in childhood ALL survivors. Hartman et al.\(^7\) was one of the first to study the measure motor performance, physical function, and PA, and to analyze the association between physical function and PA. PA was measured in 34 survivors who have been more than five years off treatment using a semi-structured interview asking the child and parents about their physical education and sporting participation. Twenty-nine children attended physical education classes and twenty-two children played sports at club level after school. The standard deviation scores for 6MWT were not different between children who did or did not participate in sports. This study did not analyze if motor performance was different between those who did or did not
participate in sports, but found a weak positive correlation between the 6MWT and motor performance.

Taskinen et al.\textsuperscript{14} measured muscle performance of 45 childhood ALL survivors who did not receive a stem cell transplant (median age of 13.3 years), and who have been at least three years off treatment (median time off treatment 6.8 years), and compared them to age-specific healthy controls ($n = 522$) and non-cancer patients who had received a stem cell transplant ($n = 94$, median age of 12.0 years, and median time after therapy of 5.2 years). Muscle performance was assessed using a battery of tests focusing on muscular endurance, strength, flexibility, and speed. PA levels were measured using a personal interview asking about their exercise routine and sports club membership. Individual muscle performance tests and overall scores for the muscle performance battery in ALL patients who did not receive stem cell transplants were not significantly different from healthy controls. However, ALL patients who did not receive stem cell transplant performed significantly better than patients who did receive a stem cell transplant in sit-ups, sit-and-reach, back-extension, shuttle-run, and overall score. Twenty-nine ALL patients had sports club memberships, but only 19 patients (42\%) exercised regularly at least once a week, while ten patients exercised more than three times per week. When investigating the relationship between the muscle performance tests and PA levels, compared to study participants who exercised less than three times per week, study patients who exercised more than three times per week had better overall scores for muscular performance and scores for individual muscular endurance, strength, flexibility and speed tests, with the exception of the leg lifts.

Hoffman et al.\textsuperscript{13} measured PA using the Past-Year Leisure-Time Physical Activity section of the Modifiable Activity Questionnaire to quantify minutes of PA per week and studied
its association with physical function using the 6MWT within five years after diagnosis. PA was not significantly different between survivors and siblings, but was related to physical function measures, including the 6MWT. Greater reported minutes of week per PA was associated with longer 6MWD (correlation coefficient and p-value statistics not reported).

Chung et al.\textsuperscript{12} studied the impact of cancer and its treatment on PA levels and behaviour in Hong Kong Chinese childhood cancer survivors ages 9 – 16 years old who have completed treatment for at least six months. The study used self-report PA questionnaires, the Chinese University of Hong Kong: PA Rating for Children and Youth (modified from the Jackson Activity Coding and Godin-Shephard Activity Questionnaire Modified for Adolescents), to retrospectively measure their PA levels before diagnosis and PA levels at the time of participation in the study. A self-reported, open-ended qualitative question was included to explore the factors affecting PA levels, namely asking the children, “Can you tell me what the factors are that influence your PA level or behavior?” The study included 128 childhood cancer survivors (mean age not reported) and 64.1\% of survivors had been diagnosed with leukemia. The majority had completed treatment in the past 24 months (64.8\%). PA levels at the time of study assessment were significantly decreased from the PA levels retrospectively reported for the prior to diagnosis time point. The study found that 37.5\% of children were not regularly active. While 58.6\% were physically active, the children were not regularly active three to five times a week. In the open-ended questions, 35.2\% of participants reported that physical factors such as fatigue and decrease in self-reported physical strength and endurance prevented them from engaging in PA. Furthermore, 41.4\% of children reported concerns that academic performance interfered with PA engagement, such as: “Too much homework and not enough time for PA”;}
“Need to make extra efforts to catch up with peers after remission”; and “Pressure to attend academic-related classes or extracurricular activities during the weekend”.

1.6.2 Psychological Factors Associated with PA in ALL Survivors

Regarding psychological factors affecting PA in children treated for ALL, self-efficacy and parental influence are the two main factors discussed in the research literature\(^7^3\). Although the focus on this thesis is not on psychological factors, such factors are important when studying PA in childhood cancer patients and survivors and will be acknowledged in the current thesis by including some relevant information from the current literature.

Self-efficacy is defined as the belief in one’s ability to organize and execute the course of action required to produce a given attainment\(^7^4\). Self-efficacy beliefs are one of the most significant predictors of success in individuals and are thought to be the primary motivator and determinant of human behaviour\(^1^0,7^5\). The perceptions of self-efficacy are shaped by four principle sources: verbal persuasion from significant others; past performance; modeling or vicarious experiences; and physiological or physical state. PA self-efficacy refers to a person’s beliefs in their own ability to perform PA\(^7^4\). PA self-efficacy can include three different components: ability for someone to overcome barriers to PA, ability to ask someone for help to be physically active, and perception of self-competence and capacity to be physically active\(^7^4\). PA self-efficacy is a significant predictor of being physically active, and can significantly influence PA behaviours in healthy populations\(^7^6\).

Few studies have investigated psychological factors influencing PA levels in children treated for childhood cancers. Finnegan et al.\(^6^4\) studied correlates of PA in 117 young adult childhood cancer survivors (mean age 24 years old with an average time off treatment of 11 years), including self-efficacy for PA measured with an 18-item questionnaire capturing six-
subscales of self-efficacy, and PA was measured using a single-item question asking how long participants have been engaging in regular moderate or vigorous PA. The study found participants who were physically active within the last six months or for more than six months had higher PA self-efficacy than survivors who were considered inactive.

Keats et al.\textsuperscript{77} studied PA behaviours in 59 adolescent cancer survivors of mixed diagnosis. The Godin Leisure Time Exercise Questionnaire (GLTEQ) was used to collect self-report information on usual PA, and self-efficacy was assessed using self-report questionnaires. Self-report PA behaviour was significantly correlated with PA self-efficacy. Wright et al.\textsuperscript{61} used the Children’s Self-perceptions of Adequacy in and Predilection of Physical Activity Scale, a questionnaire not based on self-efficacy constructs, to ask 99 children, who have completed treatment for ALL for at least one year, about PA. The children reported lower self-perception of adequacy to be physically active and had a lower preference (predilection) for participating in PA compared with their healthy counterparts.

A recent study by Gilliam et al.\textsuperscript{73} investigated cognitive influences of family and peer support on PA in 105 cancer survivors of mixed diagnosis who were at least one year off treatment (average age of 12.3 years; average time off treatment 4.9 years). PA was measured using the GLTEQ, while cognitive variables, such as family and peer support for PA, perceived benefits and barriers to PA, and PA self-efficacy, were measured using questionnaires. The study found peer and family support for PA to be correlated with self-report PA, which was partially mediated by self-efficacy for PA. In addition, survivors with greater PA self-efficacy were more active, and survivors who had more family and peer support for PA were likely to feel more confident in their ability to engage in PA, despite the physical and psychological effects of cancer.
1.7  The Importance of PA in Childhood Cancer Survivors

The well-established physical and psychological benefits of exercise and PA seen in healthy children with higher PA levels raises health concerns for childhood survivors of ALL\textsuperscript{78}. Decreased PA in healthy youths contributes to obesity, which can subsequently lead to other chronic diseases, such as type 2 diabetes, cardiovascular disease, and metabolic syndrome\textsuperscript{15}. Obesity has been shown to be related to poor academic performance, poor self-esteem, and negative social outcomes, such as bullying and teasing by peers\textsuperscript{15}. PA in healthy children have also been shown to be directly related to better academic performance and overall cognition\textsuperscript{79}, and sports participation in healthy children have been shown to be related to better psychological and social well-being, such as better self-esteem, self-concept, connectedness to friends, and mental health\textsuperscript{80}. PA also provides opportunities for movement, which is essential to a child’s motor and cognitive skills development and learning, such as integrating sensory, perception, actions and external feedback, and self-image\textsuperscript{15,81,82}.

Obesity, and subsequent development of diabetes mellitus and cardiovascular disease, have been identified as a potential late effect of chemotherapy in ALL childhood\textsuperscript{17} and adult survivors\textsuperscript{16}. Children with ALL are also at increased risk for low bone mineral density\textsuperscript{83} and may not reach peak bone mass\textsuperscript{84}. Based on the benefits of PA documented in healthy children, PA can potentially play a role in attenuating the risk of developing obesity and osteoporosis in children who have completed treatment for ALL\textsuperscript{78}.

1.8  PA and Exercise is Safe for Childhood Cancer Patients and Survivors

A systematic review by Huang and Ness\textsuperscript{85} reported fifteen studies using exercise interventions during or after treatment for any childhood cancer diagnosis; nine studies used supervised anaerobic, resistance and/or flexibility training with or without home-based
exercise, five used enhanced PA interventions, and one used an individualized home-based exercise program. Early evidence from these small exercise intervention studies showed improvements in cardiopulmonary fitness, muscle strength and flexibility, general physical functioning, health related quality of life, and reduced fatigue, and showed that exercise interventions did not have deleterious effects to the patients’ immune function.

Although these exercise interventions have been deemed safe and feasible, limitations within the existing literature do not allow for confident statements to be made about the specific benefits of exercise interventions during and after treatment for childhood cancers. These limitations include: a lack of data from randomized controlled trials with only four trials reported in the literature to date, small sample sizes (generally six to 38), limited diversity of cancer diagnosis (majority are ALL), and inconsistencies with exercise prescription parameters used (type, duration, frequency, and outcome measurements).
Chapter 2: Research Study

2.1 Introduction

Understanding the factors affecting PA for childhood cancer survivors will help healthcare providers provide quality care and may help lessen the severity of late effects of therapeutic interventions\(^{103}\). Motor performance has been shown to be related to PA in healthy children\(^{82}\), and physical function as measured by the 6MWT is a reflection of functional exercise capacity\(^{52}\). To our knowledge, only the three studies\(^{7,13,14}\) have investigated the physical factors associated with PA in children treated for ALL using objective methods of motor performance or physical function. However, these studies included patients well after they have completed treatment with a median years off treatment ranging from 5.2\(^{7}\) – 6.3\(^{14}\) years, or 9.3 years after diagnosis\(^{13}\).

Only one study\(^{13}\) used a PA questionnaire validated in children with chronic disease (Past-Year Leisure-Time PA section of the Modifiable Activity Questionnaire) while the other two studies\(^{7,14}\) measured PA using unstandardized interviews asking about PA and sports participation. Finally, the inclusion criteria for the age of the children included in these studies vary, with studies including children ages 9.2 – 20.1 years old\(^{14}\), 9.0 – 18.7 years old\(^{7}\), and 9 – 18 years old with a mean age of 13.5 years\(^{13}\).

To our knowledge, no study has examined motor performance and physical function exclusively in children between the ages of 8 – 13 years old within their first three years of completing treatment for ALL. Investigating PA levels, motor performance and physical function in children early after treatment will build an understanding of their PA levels, if the physical effects of treatment discussed in Section 1.3 are present, and if PA, motor performance, and physical function are associated with each other in this population. This will further inform
PA interventions for children who have just completed treatment for ALL, which has been suggested to potentially be a suitable time to re-integrate PA in habitual lifestyle\(^9\).

2.2 Purpose

The purpose of this descriptive pilot study was to examine the integration of motor performance and physical function testing as part of a long-term follow-up visit to determine if motor performance and physical function are associated with PA levels in children who have completed treatment for ALL within the last 3 – 36 months.

2.3 Objectives and Hypothesis

The primary objective of the current study was to determine the association between motor performance and physical function and self-report PA levels in children who have completed treatment for ALL.

_We hypothesize lower self-report PA levels will be associated with lower motor performance and lower physical function in children who have completed treatment for ALL._

2.4 Methods

2.4.1 Ethical Approval

Ethical approval for this study was provided by the Children’s and Women’s Research Ethics Board (H13 - 01823). This study was also approved by the Pediatric Hematology, Oncology, and Bone Marrow Transplant Program Research Oversight Committee at the British Columbia Children’s Hospital.

2.4.2 Participants

2.4.2.1 Population

A cross-sectional sample of children ages 8 – 13 years old and who have completed primary treatment for ALL were recruited through the oncology Long-term Follow-up Clinic
(LTFU) in the Ambulatory Care Building at the British Columbia Children’s Hospital (BCCH). The inclusion criteria were: children who were 3 – 36 months post-treatment for ALL attending the LTFU at BCCH; children knowledgeable in English to complete the questionnaires and assent forms, with parents/guardians knowledgeable in English to complete the consent forms; and children treated for ALL at BCCH. Children were excluded if they had any symptoms or impairments unrelated to the cancer diagnosis and treatment which can influence physical function or motor performance, such as Down Syndrome or limb salvage surgery; patients who received cranial radiation; patients who had a relapse; or patients who were participating in other research studies.

2.4.2.2 Recruitment

Potential participants were identified from the ALL oncology LTFU patient list. Using the eligibility criteria listed above, a list of potential participants was developed by the clinical research associates in the Pediatric Hematology, Oncology, and Bone Marrow Transplant Program. LTFU clinic nursing staff (Angela Pretula and Marion Nelson) pre-screened the list for eligible participants. The updated list was then provided to the study Co-Principal Investigator (Dr. Pritchard) or Co-Investigator (Dr. Fryer) to confirm with the treating oncologists their approval to invite the patient to participate in the study. For the potential participants approved by the treating physician, a letter of invitation was mailed to parents of the eligible potential participants approximately one month prior to their next scheduled appointment to the LTFU. A follow-up phone call was completed by the student investigator approximately 10 – 14 days later to ask if the parents were interested in participating and to answer any questions about the study. If the parents and child were interested, a study assessment visit was scheduled as part of the next LTFU clinic visit. At that time, a copy of the informed consent and
assent for parent and child, respectively, was sent by mail or email (based on parent preference), for review prior to the LTFU clinic visit. The student investigator arranged to meet the parents and participants at the LTFU clinic before escorting them to complete testing at an examination room in the Physical Therapy and Occupational Therapy Department located in the same Ambulatory Care building at BCCH.

### 2.4.2.3 Sample Size

ALL is the most commonly diagnosed malignancy in childhood cancers\(^1\) with the total number of diagnosis for ALL in children in British Columbia is approximately 30 diagnoses per year. The majority of patients in British Columbia is treated at BCCH and attends the LTFU yearly after treatment completion (approximately five patients per week). With the recruitment window of children who have completed treatment in the past 3 – 36 months, the overall recruitment pool was approximately 75 children over one year. The number of participants for this pilot study was not based on a sample size calculation, but rather aimed to recruit a representative sample of patients returning to the LTFU within an eight month period. An anticipated recruitment rate of approximately 50% of the eligible pool allowed recruitment of a final sample size of approximately ten patients into the study. The anticipated recruitment target was based the willingness of children and the parents of a clinical population to participate in additional testing and prolonged clinic visit.

### 2.5 Procedures

Depending on participant and parent preference, the study visit was scheduled prior to or after the LTFU clinic visit appointment with the physician. In addition, some testing was completed while participants were waiting for their clinic visit within an appropriate time window confirmed with the clinic nurses. At the study visit, informed consent and assent from
the parents and child, respectively, were obtained (five minutes). After informed consent and assent were obtained, the child was taken to the examination room located in the Physical and Occupational Therapy Department to complete: 1) the motor performance test (15 minutes), 2) PA questionnaire (15 minutes), and 3) fatigue questionnaire (10 minutes). The child then walked with the student investigator to the walk-way connecting the Ambulatory Care building and the main BCCH building (approximately one minute walk from the LTFU) to complete the physical function test (15 minutes). The exact order of testing was not standardized other than ensuring the physical function test was always done after the motor performance test to ensure fatigue would not affect the participants’ motor performance. The questionnaires were completed at convenient intervals during the visit. The total study testing time at the clinic visit, including obtaining consent and assent attainment (five minutes), objective measures testing (30 minutes) and child questionnaires (25 minutes), was 60 minutes.

At completion of the study visit, a copy of the Canadian Physical Activity Guidelines prepared by the Canadian Society for Exercise Physiology was given to the participants. All parents/guardians received $10.00 as compensation for cost of parking during participation in the study appointment.

2.5.1 Demographics Data

The following patient information was collected from the patient medical charts: height, weight, year and month of birth, date of diagnosis, date of treatment completion, date of clinic visit (study date), the total dose of anthracyclines in milligrams per metre squared (mg/m²), ALL risk level, and patient sex. This information was used to determine the current age, age at diagnosis, time from diagnosis to study date, and time from treatment completion to study date. The height and weight on the study date measured at the LTFU by the clinic nursing staff on the
day of the study assessment was used to determine body mass index (BMI). This information was obtained by the student investigator under the direction of Dr. Pritchard.

2.5.2 Outcome Measures

A summary of the outcome measures can be found at the end of this sub-sub-section on Table 1.

2.5.2.1 Questionnaires

2.5.2.1.1 Physical Activity Questionnaire for Older Children (PAQ-C)

PA was measured using the PA Questionnaire for Older Children\(^{104}\) (PAQ-C). The PAQ-C is a 10-item questionnaire designed for children ages 8 – 14 years assessing moderate to vigorous PA levels for the last seven days during a regular school day and weekend. The first question contains a checklist of 22 common leisure and sport PA and two “other” fields asking often they participated in these activities. This question is scored as the average of all activities under a 1 – 5 scale, 1 being “No”, 2 being “1-2”, 3 being “3-4”, 4 being “5-6”, and 5 being “7 times or more.” The other eight questions ask how often they were very active in their physical education classes, recess, lunch, after school, evenings, and weekends, and was scored using a 1 – 5 scale. The total score is an average of the sum of the nine questions ranging from 1 – 5, with 1 indicating low PA and 5 indicating high PA. The Chronbach’s alpha coefficient of internal consistency was reported as \(r = 0.73\) for all age groups\(^{105}\), while validity against a Caltrac motion sensor has been reported with a correlation of \(r = 0.39\)^{106}. Depending on the participant’s literacy, the questionnaire took approximately 15 minutes to complete.

2.5.2.1.2 PedsQL™ – Multidimensional Fatigue Scale

Cancer-related fatigue was measured using the PedsQL™ Multidimensional Fatigue Scale. Permission to use this questionnaire was requested by completing the standard permission
request forms found in their website (www.pedsqol.org). This 18-item questionnaire captures three dimensions of fatigue: (1) General Fatigue (GF) (e.g., “I feel too tired to spend time with my friends.”), (2) Rest/Sleep Fatigue (SRF) (e.g., “I take a lot of naps.”), and (3) Cognitive Fatigue (CF) (e.g., “It is hard for me to keep my attention on things.”), with six items for each dimension. The participant is asked to grade how often they find problems with fatigue with the respective items using a Likert scale of 0 – 4, with 0 being “Never”, 1 being “Almost Never”, 2 being “Sometimes”, 3 being “Often”, and 5 being “Always”. The questionnaire is available in a child (8 – 12 years old) and teen (13 – 18 years old) self-report version, and in parent proxy version. All versions differ only in instructional prompting, but all 18 items are identical in all versions. The questionnaire asks the participant to rate fatigue related problems in the past month. The questionnaire is scored out of 100, with higher score indicating better health-related quality of life (lower fatigue symptoms). The questionnaire has been tested for construct validity against healthy children (p = 0.0001 for the total fatigue score and GF, p = 0.005 for SRF, and p = 0.024 for CF), and internal consistency reliability (Chronbach coefficient alpha of 0.88 for total score, 0.77 for GF, 0.74 for SRF, and for CF for child-report, and 0.92, 0.88, 0.87, and 0.91, respectively, for teen-report), in a pediatric cancer population\textsuperscript{107}. Depending on the participant’s literacy, the length of time to complete the questionnaire is reported to be ten minutes.

2.5.2.2 Physical Assessments

2.5.2.2.1 Bruininks-Oseretsky Test of Motor Proficiency, Second Edition – Short Form (BOT-2 SF)

Motor performance was assessed using the Short Form version of the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition\textsuperscript{108} (BOT-2 SF). The first version, Bruininks-Oseretsky Test of Motor Proficiency (BOTMP), has been used in previous studies to
assess children with childhood cancers. The BOTMP was revised using focus groups with experienced users, including occupational and physical therapists, with six improvement goals guiding the development of the BOT-2: (1) improving the relevance of the testing content; (2) expanding the range of fine and gross motor skills tested; (3) allowing better testing for younger children, ages four and five years old; (4) extending normative data with people up to ages 21 years and 11 months old; (5) improve the presentation of testing scripts for examiners and examinees; and (6) improve the quality of testing equipment. The BOT-2 is a standardized, norm-referenced measurement tool used to assess fine and gross motor skills of children and youth between the ages 4 – 21 years of age. The BOT-2 allows practitioners and researchers to discriminate and evaluate motor performance in four motor area composites: fine manual control, manual coordination, body coordination, and strength and agility. The Short Form version of the BOT-2 consists of 14 tests selected by the creator as the most representative assessments of each motor area composite. Scores can be reported as a total score, which can then be converted to a standardized score to compare against pre-determined normalized scales or percentiles. After scoring, the participants can be placed in five performance descriptive categories: “Well-Above Average”, “Above Average”, “Average”, “Below Average”, and “Well-Below Average.” The Short Form version was scored by reporting the standardized score and performance descriptive category.

The BOT-2 has been used to assess motor performance in clinical populations with developmental coordination disorders, mild to moderate mental disorders, and children with high-functioning autism or Asperger’s disorder. It successfully distinguishes between clinical and non-clinical populations by demonstrating significantly lower scores in clinical populations. Each of the tests used in the BOT-2 have been tested for inter-rater, test-retest,
and internal consistency reliability, and have been reported as, depending on the individual test, > 0.86, > 0.80, and > 0.80, respectively\textsuperscript{110}. This assessment was administered by the student investigator, and took approximately 15 minutes to complete.

\textbf{2.5.2.2.2 Six Minute Walk Test (6MWT)}

Physical function was assessed using the 6MWT, using the standardized methods outlined by the American Thoracic Society (ATS)\textsuperscript{52}. The 6MWT assesses overall aerobic endurance by having the participant walk as far as they can at a self-selected pace back and forth between two pylons. An existing 50 m course in the walkway connecting the Main Building and the Ambulatory Care building at BCCH was used, making the distance between the two pylons 25 m apart. The number of laps was counted, the distance of partial laps was measured using a tape measure, and the total distance covered within the six minutes (six-minute walk distance, 6MWD) was recorded. The only exception to the standardized methods as outlined by the ATS was the length of each lap. The ATS states each lap must be 60 m in length but the current study used an existing 6MWT course at the BCCH measuring 50 m per lap. The 6MWT has been reviewed as a good representation of sub-maximal level of functional capacity which is easy to administer and reflects functional exercise levels for daily PA. Test-retest reliability for the 6MWT in chronic pediatric conditions has been reported in a systematic review of measurement properties with an interclass correlations ranging between 0.84 – 0.98 from six studies for different chronic conditions\textsuperscript{111}. In the same systematic review, criterion validity for 6MWT was tested in one study against estimated VO\textsubscript{2max} (r = 0.34), two studies with measured VO\textsubscript{2max} (r = 0.76), and three studies with measured VO\textsubscript{2peak} (r = 0.43 – 0.53). This assessment was administered by the student investigator, and took approximately 15 minutes to complete.
Table 1 - Summary of Outcome Measures and Time to Administer

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<td><strong>Objective Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor Performance</td>
<td>Bruininks-Oseretksy Test of Motor Proficiency, Second Edition (BOT-2)</td>
<td>Bruininsk and Bruininks, 2005&lt;sup&gt;108&lt;/sup&gt;</td>
<td>15</td>
<td>Study/Clinical Staff</td>
</tr>
<tr>
<td>Physical Function</td>
<td>Six-Minute Walk Test (6MWT)</td>
<td>Bartels, Groot &amp; Terwee, 2012&lt;sup&gt;111&lt;/sup&gt;</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td><strong>Total Questionnaire Time to Administer:</strong></td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Time to Administer Objective Measures:</strong></td>
<td>30 Minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Obtaining Consent and Assent:</strong></td>
<td>5 Minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Time for Children with Consent/Assent:</strong></td>
<td>60 Minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.5.3 Statistical Analysis

Demographic, anthropometric and medical information were summarized as means and standard deviations. Participants were categorized into ALL risk level group, namely Standard Risk and High Risk, and Anthracycline Cardiotoxicity Risk groups<sup>112</sup> based on total anthracycline dosage (mg/m<sup>2</sup>), and Low Toxicity Risk (0 – 100 mg/m<sup>2</sup>), Moderate Toxicity (101 – 250 mg/m<sup>2</sup>), and High Toxicity Risk (> 250 mg/m<sup>2</sup>). Participants were also categorized into BMI group (i.e. healthy weight, overweight, and obese) based on the World Health Organization Child Growth Standards<sup>113</sup> and descriptive category for the BOT-2 SF. Outcome variables were
summarized as sample means, standard deviations and 95% confidence intervals (CI) for the child self-reported PA as PAQ-C scores; standardized scores for BOT-2 SF; the measured distance for the 6MWT (6MWD), the calculated distance of the 6MWD for healthy children, and SDS for normative data comparison developed by Geiger et al.\textsuperscript{114}; and the PedsQL™ Multidimensional Fatigue Scores as Total Fatigue, CF, SRF, and CF. The measured PedsQL™ Multidimensional Fatigue Scores was compared to the scores for childhood cancer patients (mix of on-treatment and off-treatment children) and healthy children from Varni et al.\textsuperscript{107}.

Data analysis was done using SPSS statistical software (IBM, Version 22.0) with accepted levels of significance at $p < 0.05$. The hypothesis was tested using Spearman’s correlation coefficient to test the association between PAQ-C scores and BOT-2 scores and measured 6MWD. Mann Whitney U-Test was used to test the difference in outcome variables between ALL risk level group, BMI and Anthracycline Cardiotoxicity Risk groups, and a simple linear regression model was used to test the effect size in cases where associations were found. Covariates were analyzed to test their effect on primary and secondary outcomes using Spearman’s correlations.

2.6 Results

2.6.1 Participants

At the start of recruitment a list of potential participants who would attend the LTFU clinic over the following eight month period was prepared by the LTFU Clinic clinical research associates. Twenty one potential participants were identified, and contacted regarding participation in the study. Of these, 13 children participated in the study visit. Three children were not interested in participating, three could not be contacted, one had moved away from Vancouver, and one had a conflicting appointment and could not attend the study visit.
The participant characteristics are presented in Table 2. The study participants were primarily male, with nine male participants and four female participants. The mean age of the participants at the time of the study was 9.6 years and the mean BMI was 19.2 kg/m².

2.6.2 Outcomes Measures

The means, standard deviations and 95% CI for the outcome measures are outlined in Table 3. The mean PAQ-C score was 3.1 (95% CI: 2.8 – 3.4). The mean BOT-2 SF standardized score was 50.9 (95% CI: 47.0 – 54.9) and the percentile score was 52.9 (95% CI: 55.5 – 89.0). The 95% CI for the standardized score was within the range of “Average” scores (40 – 60)\(^\text{108}\) for motor performance, and 95% CI for the percentile scores were within or above “Average” (18 – 97)\(^\text{108}\), respectively. Using descriptive categories of the BOT-2 SF, one participant was considered to perform “Below Average”, nine were “Average”, and three were “Above Average”. The mean measured 6MWD was 544.42 m (95% CI: 486.8 – 602.1 m), calculated 6MWD was 628.4 m (95% CI: 610.8 – 645.9 m) and the mean 6MWD SDS was -1.62 (95% CI: -2.53 – -0.71) with a range from -4.15 – 1.42. Two participants performed above healthy norms for the 6MWD. The 95% CI for the measured 6MWD was less than calculated 6MWD and did not overlap with the 95% CI for the calculated 6MWD. The 95% CI for the 6MWD SDS was less than 0. These results provided confidence that the mean measured 6MWD was less than the mean calculated 6MWD, and the mean 6MWD SDS was less than normative values. The mean scores from the PedsQL™ Multidimensional Fatigue Scale for Total Fatigue, GF, SRF, and CF were 74.6 (95% CI: 67.9 – 81.3), 82.7 (95% CI: 76.4 – 89.0), 70.2 (95% CI: 61.0 – 79.4), and 74.6 (95% CI: 58.5 – 83.1), respectively.

\(^{108}\)
2.6.3 Relationship of PA with Motor Performance and Physical Function

PAQ-C score was not significantly associated with BOT-2 SF standardized score ($r_s = 0.282$, $p = 0.35$), and measured 6MWD ($r_s = -0.429$, $p = 0.14$) or 6MWD SDS ($r_s = -0.094$, $p = 0.76$).

2.6.4 Impact of Body Mass Index

BMI SDS was significantly associated with measured 6MWD ($r_s = -0.602$, $p = 0.03$) and 6MWD SDS ($r_s = -0.691$, $p < 0.01$), and approached significance with BOT-2 SF standardized scores ($r_s = -0.515$, $p = 0.07$). The Mann-Whitney U test was used to test the difference in measured 6MWD, 6MWD SDS, BOT-2 standardized score, and the PAC-Q Score between the healthy weight (HW, $n = 7$) and overweight and obese (OWO, $n = 6$) children (Table 4). The one-tailed p-value statistics was used because HW children were expected to have higher scores than the OWO children for each outcome measure. The mean rank for HW children and OWO children for the measured 6MWD were 9.14 and 4.50, respectively, and a significant difference was found ($\text{Mann-Whitney U (U)} = 6.0$, $Z = -2.143$, $p = 0.04$, $r = 0.6$). The mean rank for HW and OWO children for the 6MWD SDS were 9.86 and 3.67, respectively, and a significant difference was found ($U = 1.0$, $Z = -2.857$, $p < 0.01$, $r = 0.8$). The mean rank for HW and OWO children for the BOT-2 SF standardized score were 9.00 and 4.57, respectively, and a trend towards a significant difference was found ($U = 7.0$, $Z = -2.017$, $p = 0.05$, $r = 0.6$). The mean rank for the PAQ-C Score between the HW and OWO children were 6.93 and 7.08, respectively, and no significant difference was found ($U = 20.5$, $Z = -0.072$, $p = 0.95$, $r = 0.02$). A simple linear regression model was done with BMI SDS being the independent variable and 6MWD SDS being the dependent variable. Every increase in one BMI SDS was associated with a decrease in 0.70 6MWD SDS ($\text{Constant} = -0.98$, $\beta = -0.70$, $p = 0.04$, $R^2 = 0.325$).
2.6.5 Impact of ALL Risk Level

The Mann-Whitney U test was used to test the difference in measured 6MWD, 6MWD SDS, BOT-2 standardized score, and the PAC-Q Score between the Standard and High Risk Level children (Table 5). No significant difference was found between the two Standard Risk (n = 9) and High Risk (n = 4) children. However, the mean PAQ-C score (U = 8.0, Z = -1.545, p = 0.15, r = 0.4), measured 6MWD (U = 10.0, Z = -1.234, p = 0.26, r = 0.3), 6MWD SDS (U = 10.0, Z = -1.234, p = 0.26, r = 0.3), and BOT-2 SF standardized score (U = 18.0, Z = 0, p = 1.00, r = 0) for the Standard Risk children were greater but not statistically different than the High-Risk children.

2.6.6 Impact of Anthracycline Dosage and Cardiotoxicity Risk Category

The average cumulative anthracycline dosage for the current study was 105.8 mg/m², with nine participants categorized as Low Toxicity Risk for cardiotoxicity, and four participants categorized as Moderate Toxicity Risk. Anthracycline dosage was not associated with PAQ-C Scores ($r_s = 0.469$, $p = 0.11$), BOT-2 SF standardized scores ($r_s = -0.229$, $p = 0.45$), or fatigue scores (GF $r_s = 0.152$, $p = 0.62$; SRF $r_s = 0.266$, $p = 0.38$; CF $r_s = 0.089$, $p = 0.77$; Total Fatigue $r_s = 0.197$, $p = 0.51$). However, there was a trend for an association between anthracycline dosage and measured 6MWD ($r_s = -0.492$, $p = 0.09$), but not for 6MWD SDS ($r_s = -0.369$, $p = 0.22$). The Mann-Whitney U test was used to test the difference in measured 6MWD, 6MWD SDS, BOT-2 standardized score, and the PAC-Q Score between the anthracycline cardiotoxicity risk categories (Table 6). No significant difference was found between the Low Toxicity (n = 9) and Moderate Toxicity (n = 4) children. The mean measured 6MWD, 6MWD SDS, and BOT-2 standardized score for the Low Risk children were greater but not statistically different than the Moderate Risk children.
2.6.7 Impact of Time from Treatment Completion

Time from treatment completion was not associated with PAQ-C ($r_s = 0.165$, $p = 0.59$), BOT-2 SF standardized scores ($r_s = 0.477$, $p = 0.12$), measured 6MWD ($r_s = 0.440$, $p = 0.13$) and 6MWD SDS ($r_s = 0.434$, $p = 0.14$), or fatigue scores (GF $r_s = 0.265$, $p = 0.38$; SRF $r_s = 0.248$, $p = 0.41$; CF $r_s = 0.077$, $p = 0.80$, Total Fatigue $r_s = 0.283$, $p = 0.35$).
<table>
<thead>
<tr>
<th>Table 2 - Participant Characteristics</th>
<th>Mean (SD) or n (%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>4 Female (31%); 9 Male (69%)</td>
<td></td>
</tr>
<tr>
<td>Age at Study Session (years)</td>
<td>9.6 (1.4)</td>
<td>8.3 – 13.7</td>
</tr>
<tr>
<td>Age at Diagnosis (years)</td>
<td>5.0 (1.7)</td>
<td>2.6 – 8.8</td>
</tr>
<tr>
<td>Time from Diagnosis (years)</td>
<td>5.1 (0.9)</td>
<td>2.9 – 6.2</td>
</tr>
<tr>
<td>Time from Treatment Completion (years)</td>
<td>2.1 (0.7)</td>
<td>0.7 – 3.2</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td>19.2 (3.6)</td>
<td>14.5 – 26.0</td>
</tr>
<tr>
<td>Healthy</td>
<td>7 (54%)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>3 (24%)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>3 (24%)</td>
<td></td>
</tr>
<tr>
<td>SDS</td>
<td>0.9 (1.2)</td>
<td>-1.44 – 3.00</td>
</tr>
<tr>
<td>Percentile</td>
<td>72.2 (28)</td>
<td>8 – 99</td>
</tr>
<tr>
<td><strong>ALL Risk Level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Risk</td>
<td>9 (69%)</td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>4 (31%)</td>
<td></td>
</tr>
<tr>
<td><strong>Anthracycline Dosage (mg/m^2)</strong></td>
<td>105.7 (44.7)</td>
<td>75 – 175</td>
</tr>
<tr>
<td>Low Toxicity Risk</td>
<td>9 (69%)</td>
<td></td>
</tr>
<tr>
<td>Moderate Toxicity Risk</td>
<td>4 (31%)</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: BMI: body mass index; ALL: acute lymphoblastic leukemia.*
<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Mean (SD) or n (%)</th>
<th>Range</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAQ-C Score</td>
<td>3.1 (0.5)</td>
<td>2.2 – 3.6</td>
<td>2.8 – 3.4</td>
</tr>
<tr>
<td>PedsQL™ Multidimensional Fatigue Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Fatigue Score</td>
<td>74.6 (11.1)</td>
<td>51.4 – 95.8</td>
<td>67.9 – 81.3</td>
</tr>
<tr>
<td>General Fatigue</td>
<td>82.7 (10.5)</td>
<td>66.7 – 100.0</td>
<td>76.4 – 89.0</td>
</tr>
<tr>
<td>Sleep/Rest Fatigue</td>
<td>70.2 (15.3)</td>
<td>37.5 – 91.7</td>
<td>61.0 – 79.4</td>
</tr>
<tr>
<td>Cognitive Fatigue</td>
<td>74.6 (11.1)</td>
<td>41.7 – 100.0</td>
<td>58.5 – 83.1</td>
</tr>
<tr>
<td>6 Minute Walk Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measured 6MWD (m)</td>
<td>544.4 (95.4)</td>
<td>409.72 – 735.19</td>
<td>486.8 – 602.1</td>
</tr>
<tr>
<td>Calculated 6MWD (m)</td>
<td>628.4 (29.0)</td>
<td>588.3 – 688.4</td>
<td>610.8 – 645.9</td>
</tr>
<tr>
<td>6MWD SDS</td>
<td>-1.62 (1.50)</td>
<td>-4.15 – 1.42</td>
<td>-2.53 – -0.71</td>
</tr>
<tr>
<td>Below Norm</td>
<td>11 (85%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above Norm</td>
<td>2 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOT-2 SF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standardized Score</td>
<td>50.9 (6.5)</td>
<td>40.0 – 61.0</td>
<td>47.0 – 54.9</td>
</tr>
<tr>
<td>Percentile Score</td>
<td>52.9 (22.5)</td>
<td>16.0 – 86.0</td>
<td>55.5 – 89.0</td>
</tr>
<tr>
<td>BOT-2 Descriptive Category</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Below Average</td>
<td>1 (8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>9 (69%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above Average</td>
<td>3 (23%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PAQ-C: Physical Activity Questionnaire for Older Children; 6MWD: 6 minute walk distance; BOT-2 SF: Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition Short Form; SDS: standard deviation score.
Table 4 – Means and Mann-Whitney U Test statistics in Outcome Measures between Healthy Weight and Overweight/Obese Children

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>Mean</th>
<th>Mean Ranks</th>
<th>U</th>
<th>Z</th>
<th>Effect size, r</th>
<th>1-tailed P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HW n = 7</td>
<td>OWO n = 6</td>
<td>HW n = 7</td>
<td>OWO n = 6</td>
</tr>
<tr>
<td>6MWD SDS</td>
<td>-0.63</td>
<td>-2.78</td>
<td>9.86</td>
<td>3.67</td>
<td>1.0</td>
<td>-2.857</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>595.9</td>
<td>484.3</td>
<td>9.14</td>
<td>4.50</td>
<td>6.0</td>
<td>-2.143</td>
</tr>
<tr>
<td>BOT-2 SF Standardized Score</td>
<td>54.7</td>
<td>46.5</td>
<td>9.00</td>
<td>4.57</td>
<td>7.0</td>
<td>-2.017</td>
</tr>
<tr>
<td>PAQ-C</td>
<td>3.1</td>
<td>3.1</td>
<td>6.93</td>
<td>7.08</td>
<td>20.5</td>
<td>-0.072</td>
</tr>
</tbody>
</table>

Abbreviations: HW: healthy weight, OWO, overweight or obese; PAQ-C: Physical Activity Questionnaire for Older Children; 6MWD: 6 minute walk distance; BOT-2 SF: Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition Short Form; SDS: standard deviation score.

Table 5 – Means and Mann-Whitney U Test Statistics for Outcome Measures between ALL Risk Level Groups

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>Mean</th>
<th>Mean Ranks</th>
<th>U</th>
<th>Z</th>
<th>Effect size, r</th>
<th>1-tailed P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Standard Risk n = 9</td>
<td>High Risk n = 4</td>
<td>Standard Risk n = 9</td>
<td>High Risk n = 4</td>
</tr>
<tr>
<td>6MWD SDS</td>
<td>-1.28</td>
<td>-2.39</td>
<td>7.89</td>
<td>5.00</td>
<td>10.0</td>
<td>-1.234</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>563.2</td>
<td>502.1</td>
<td>7.89</td>
<td>5.00</td>
<td>10.0</td>
<td>-1.234</td>
</tr>
<tr>
<td>BOT-2 SF Standardized Score</td>
<td>51.7</td>
<td>49.3</td>
<td>7.00</td>
<td>7.00</td>
<td>18.0</td>
<td>0</td>
</tr>
<tr>
<td>PAQ-C</td>
<td>3.0</td>
<td>3.3</td>
<td>5.89</td>
<td>9.50</td>
<td>8.0</td>
<td>-1.545</td>
</tr>
</tbody>
</table>

Abbreviations: PAQ-C: Physical Activity Questionnaire for Older Children; 6MWD: 6 minute walk distance; BOT-2 SF: Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition Short Form; SDS: standard deviation score.
Table 6 - Means and Mann-Whitney U Test Statistics for Outcome Measures between Anthracycline Cardiotoxicity Risk Groups

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>Mean</th>
<th>Mean Ranks</th>
<th>U</th>
<th>Z</th>
<th>Effect size, r</th>
<th>1-tailed P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Toxicity n = 9</td>
<td>Mod. Toxicity n = 4</td>
<td>Low Toxicity n = 9</td>
<td>Mod. Toxicity n = 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWD SDS</td>
<td>-1.48</td>
<td>-1.95</td>
<td>7.56</td>
<td>5.75</td>
<td>13.0</td>
<td>-0.772</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>565.0</td>
<td>498.0</td>
<td>8.00</td>
<td>4.75</td>
<td>9.0</td>
<td>-1.389</td>
</tr>
<tr>
<td>BOT-2 SF Standardized Score</td>
<td>52.9</td>
<td>46.6</td>
<td>7.78</td>
<td>5.25</td>
<td>11.0</td>
<td>-1.089</td>
</tr>
<tr>
<td>PAQ-C</td>
<td>3.0</td>
<td>3.3</td>
<td>6.06</td>
<td>9.13</td>
<td>9.5</td>
<td>-1.313</td>
</tr>
</tbody>
</table>

Abbreviations: PAQ-C: Physical Activity Questionnaire for Older Children; 6MWD: 6 minute walk distance; BOT-2 SF: Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition Short Form; SDS: standard deviation score.
Figure 1 - Scatter Plot of PAQ-C Scores and BOT-2 SF Standardized Scores

Abbreviations: PAQ-C: Physical Activity Questionnaire for Older Children; BOT-2 SF: Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition Short Form.
Figure 2 - Scatter Plot of PAQ-C Scores and 6MWD SDS

Abbreviations: PAQ-C: Physical Activity Questionnaire for Older Children; 6MWD: 6 minute walk distance; SDS: standard deviation score.
Chapter 3: Conclusion

3.1 Primary Objective and Hypothesis

The primary objective of this pilot study was to examine if motor performance and physical function are associated with PA levels in children ages 8 – 13 years old who have completed treatment for ALL within the last 3 – 36 months. The hypothesis was lower PA levels would be associated with lower motor performance and lower physical function. In the current study, PA was not associated with motor performance, using the BOT-2 SF, or physical function, using the 6MWT. To our knowledge, this is the first study to have characterized and studied the association between motor performance, physical function, and PA in children who have recently completed treatment for ALL. The lack of observed association may be due to a small sample size of 13 participants, or may also suggest self-report PA levels may not be strongly associated with objective measures of motor performance or physical function in children who have completed treatment for ALL. The lack of observed association may also suggest PA levels in these children are influenced by other factors, such as parental/peer support and self-efficacy in children shortly after completing treatment.

3.2 Effect of BMI on Outcome Measures

Seven participants (54%) had a BMI in the healthy weight range, and six participants (46%) were overweight or obese. The percentage of participants who were overweight or obese was higher than observed in the general population of children in Canada. Using data from 2009 – 2011 Statistics Canada\textsuperscript{115} for children between ages of 5 – 17 years old, 20% of children were overweight and 12% were obese (32% total).

In the current study, children categorized as healthy weight children performed better for their age group in both the BOT-2 SF and 6MWT compared with children who were overweight.
and obese. In addition, the 6MWD SDS was significantly correlated with BMI SDS, where an increase in one BMI SDS was associated with a decrease in 0.70 6MWD SDS. This observed relationship between BMI and 6MWT is consistent with previous studies in healthy children and children who have completed treatment for ALL. Geiger et al.\textsuperscript{114} reported that healthy children with higher BMI had lower 6MWDs, and Hartman et al.\textsuperscript{7} found a weak negative association between BMI SDS and 6MWD SDS. The difference in BOT-2 SF standardized score between healthy weight children and children who were overweight or obese trended towards significance. In children with a cancer diagnosis, increased BMI has been shown to be related to reduced motor performance\textsuperscript{116}. Finally, no difference in PA levels was found between children who were healthy weight and children who were overweight or obese, which was similar to the findings from Florin et al.\textsuperscript{66} study on PA in adult survivors of childhood ALL.

3.3 Relationship of PA with Motor Performance and Physical Performance

Although motor performance has been shown to be associated with PA levels in healthy children\textsuperscript{49,82}, only a few studies have recently examined the association of PA with motor performance and physical function in children who have completed treatment for ALL. The results to date have been inconsistent. Similar to the current study, Hartman et al.\textsuperscript{7} found no significant difference in 6MWD between children who did and did not participate in sports in 34 children who completed treatment for ALL. The study measured motor performance, but did not analyze its association with sports participation. Contrary to the current study, Taskinen et al.\textsuperscript{14} studied 45 childhood ALL survivors and found an association between self-report PA and physical function. Children who reported exercising more than three times per week had better overall muscle performance measures than children who reported exercising less than three times per week. Muscle performance was assessed by six physical performance tests administered by a
physiotherapist, namely the leg-lift, repeated squatting, sit-up, sit-and-reach, back extension, and shuttle run tests. Hoffman et al.\textsuperscript{13} found an association between PA and 6MWD, where children who reported more minutes of weekly PA had greater 6MWD. Chung et al.\textsuperscript{12} used a self-report PA questionnaire and an open-ended question to investigate the factors affect PA levels in childhood cancer survivors of mixed diagnosis in Hong Kong and found PA levels to be lower in these survivors, and physical factors, such as self-reported fatigue and self-reported decrease in physical strength and endurance, were reasons for lowered PA levels, as well as prioritizing academic performance over PA.

3.4 Comparison of Outcome Measures with Published and Normative Data

3.4.1 Physical Activity

The PA levels observed in the current study were comparable to those observed in a previous study of non-cancer children in United Kingdom\textsuperscript{117} and Canada\textsuperscript{118}, which also used the Physical Activity Questionnaire for Older Children. Tomlin et al.\textsuperscript{119} used the same measure to capture sports participation and examined sport drinks consumption in children without a cancer diagnosis. This cross-sectional study separated children into two groups, namely children who participated in organized sports and those who did not. The study participants were school aged children with an average age of 9.9 years in the non-sports group and 9.9 years in the sports group. In the non-sports group (n = 295 females and 204 males) scored 2.9 on the PAQ-C, and the sports group (n = 441 females and 445 males) scored 3.3. Participants in the current study scored an average of 3.1, which was lower than the group of healthy children who participated in organized sport. However, the 95% CI for the PAQ-C Score in the current study was 2.8 – 3.4, which includes both the non-sport group and sport group. These results did not provide confidence to conclude if participants in the current study were comparable to the non-sport
group or sport group. Furthermore, the designation of group, either non-sport or sport, was based on a single question asking whether or not children participated in organized sports. The authors of the study noted a limitation of using this method to measure sport participation was that it does not provide information on the quality of PA\textsuperscript{119}.

Previous studies have found PA levels in childhood ALL patients and survivors to be lower compared to their healthy counterparts. Chung et al.\textsuperscript{12} found significantly lower PA levels from before diagnosis to time of study participation (64.8% of participants having been off treatment for 24 months) in childhood cancer survivors of mixed diagnosis. Winter et al.\textsuperscript{9} completed a systematic review and found five studies measuring PA after treatment (1.5 years to 10 years from treatment). A reduced levels of PA was observed compared with healthy controls in three studies with self-report measures\textsuperscript{60,61,63}, one with heart-rate monitors\textsuperscript{59}, and one with accelerometers\textsuperscript{62}.

### 3.4.2 Motor Performance

The current study showed similar results to previous studies who have characterized motor performance in ALL survivors using the BOT-2. Ramchandren et al.\textsuperscript{37} used the first edition of the BOT and found 5\% of patients performed below average compared with standardized norms, which is consistent with the findings of the current study, in which one participant performed below average (8\%). De Luca et al.\textsuperscript{50} used the BOT-2 SF and found 16.2\% (6/37) of participants performed below average, which is consistent with the percentage of people with motor impairments (17\%) in the normal population. However, the average standardized BOT-2 SF score in the De Luca study was 51, which is comparable to the average standardized score of 50 observed in the current study.
In addition, the 95% CI for the BOT-2 SF standardized score were within the range of “Average” score (40 – 60)\(^{108}\) for motor performance, which suggests the motor performance of ALL children in the current study was “Average.”

For studies using the Movement Assessment Battery for Children (MABC), the systematic review by Green et al.\(^{32}\) included five studies, and reported 25 – 54% of participants had gross or fine motor impairments. In a more recent study, not included in the review and also used the MABC-2, De Luca et al.\(^{50}\) reported 27% (10/37) of participants performing lower than norms. Hartman et al.\(^{7}\) used the MABC-2, and reported 38% (10/34) of participants were “at risk for impairment” at end of treatment, but performed with normal scores at 5-year follow-up. Only one participant was reported to be “at risk for impairment” at end of treatment and 5-year follow-up.

Other motor performance measurement tools have been used in children with ALL. Beulertz et al.\(^{51}\) used the MOT 4-6 and the DMT 6-18 to test motor performance in children ages 4 – 6 years old and 6 – 18 years old, respectively. While 27% of all participants’ performance below average, all children ages 4 – 6 performed normal and 34% of children ages 6 – 17 performed below average. Leone et al.\(^{49}\) reported 48.2% of participants were found to have impairments in gross motor skills using the University of Quebec in Chicoutimi and Montreal (UQAC-UQAM) motor skills battery tests.

A previous study\(^{50}\) and the current study used the BOT-2, or the first edition of the BOT\(^{37}\), and found lower incidences of motor performance impairment compared to studies who have used the MABC-2 or other motor performance measurement tools. This observation supports the work of De Luca et al.\(^{50}\) who proposed the BOT-2 SF is not as sensitive a measure of motor performance as the MABC-2. De Luca et al.\(^{50}\) reasoned the BOT-2 SF was designed as
a screening assessment and is considered to have purer, relatively simple, repetitive motor tests. In contrast, MABC-2, which includes motor skill tests requiring stronger motor planning and cognitive effort, may be more sensitive to the subtle impairments reported in childhood ALL survivors\textsuperscript{50}. Furthermore, the differences in assessment tools make it difficult to compare the results across studies using other assessment tools.

The current study did not find a significant difference in motor performance by ALL risk level group or anthracycline cardiotoxicity groups. This finding was similar to Hartman et al.\textsuperscript{7}, where treatment regimens had no effect on motor performance at the end of treatment. However, at 5-year follow-up, Hartman et al.\textsuperscript{7} found High Risk children had significantly better motor performance compared with Non-High Risk children. Taskinen et al.\textsuperscript{14} also found no significant difference with individual muscle performance tests and overall muscle performance between ALL risk level group.

### 3.4.3 Physical Function

For the 6MWT, the 95% CI for the measured 6MWD fell below the 95% CI for the calculated 6MWD, and the 95% CI 6MWD SDS was less than 0, both of which suggested the ALL children in the current study did not walk as far and had lower physical function compared with healthy children. The 6MWT results in the current study are consistent with previous studies in showing impairment in physical function in many childhood cancer survivors. Hartman et al.\textsuperscript{7} found all 34 ALL participants walked a shorter distance compared with normative values an average of 5.2 years after treatment. Hoffman et al.\textsuperscript{13} studied 183 patients of mixed cancer diagnosis, and reported patients had a lower 6MWD by 27 m compared to siblings. Hooke et al.\textsuperscript{55} tested children who were on treatment for ALL and followed them throughout
treatment cycles. After three treatment cycles, 93% of patients performed one or more standard deviations below the norm.

3.5 Fatigue

Based on the study results, it could not be concluded if the children in the current study were fatigued after completing treatment for ALL. The mean scores from the PedsQL™ Multidimensional Fatigue Scale for Total Fatigue, GF, SRF, and CF were 74.6 (95% CI: 67.9 – 81.3), 82.7 (95% CI: 76.4 – 89.0), 70.2 (95% CI: 61.0 – 79.4), and 74.6 (95% CI: 58.5 – 83.1), respectively. Varni et al.\textsuperscript{107} tested the validity and reliability of the PedsQL™ Multidimensional Fatigue Scale in 220 childhood cancer patients and survivors of mixed diagnoses (50% leukemia patients) ages 5 – 18 years old (mean age not reported). The mean scores from the PedsQL™ Multidimensional Fatigue scores for children who were off treatment for more than 12 months for Total Fatigue, GF, SRF, and CF were 74.6, 79.3, 72.8, and 71.63, In the same study, the scores for children without a cancer diagnosis for Total Fatigue, GF, SRF, and CF were 80.5, 85.3, 75.0, and 81.1, respectively. The scores for overall fatigue and the three dimensions of fatigue between children without a cancer diagnosis and children who were off treatment were not statistically different. The mean scores from the PedsQL™ Multidimensional Fatigue scores for on-treatment children for Total Fatigue, GF, SRF, and CF were 68.5, 71.4, 63.43, and 70.8, respectively. Although the mean scores for overall fatigue and all three fatigue dimensions for the children off treatment for 12 months and children without a cancer diagnosis were both within the 95% CI for the mean scores for the current study, the mean scores for Total Fatigue, SRF, and CF for children on treatment also fell within the 95% CI. These results did not provide confidence to conclude that the measured fatigue scores for the current study were comparable to the scores of the childhood cancer patients or to the children without a cancer diagnosis in the
Varni et al.\textsuperscript{107} study. Therefore, whether or not the children in the current study were fatigued after completing treatment for ALL was unclear.

The current study did not find fatigue to be associated with PA, motor performance, and physical function, which was inconsistent with the findings from previous studies. Fatigue has been suggested to be a significant symptom related to cancer treatment for ALL that can interfere with childhood developmental experiences and engagement in PA while the children are undergoing treatment\textsuperscript{46}. Hooke et al.\textsuperscript{54} reported that 6MWD increased when fatigue levels decreased in children and adolescents receiving chemotherapy treatment. An observational study investigating chronic fatigue in 102 long-term survivors of childhood lymphomas and leukemia found survivors with persistence chronic fatigue had reduced PA levels\textsuperscript{120}. Hooke et al.\textsuperscript{55} observed an overall decrease in self-report fatigue from the first to the third cycle of treatment. The authors suggested this decrease in fatigue was because the third cycle of treatment does not include dexamethasone, which has been known to be associated with fatigue in ALL patients during treatment\textsuperscript{26}, and the side effects would have diminished during the third cycle of treatment\textsuperscript{54}. Although fatigue has been reported in long-term survivors of childhood ALL\textsuperscript{120}, the inconclusive data regarding whether or not the current study participants were fatigued may have influenced the ability to detect an association between fatigue PA, motor performance, and physical function.

\textbf{3.6 Study Strengths}

The current study had several strengths. First, to our knowledge, the current study was the first to use validated measurement tools to investigate the association between PA, motor performance, and physical function. Only one study\textsuperscript{13} used a PA questionnaire validated in health populations and children with chronic disease (Past-Year Leisure-Time Physical Activity
section of the Modifiable Activity Questionnaire). The other two studies\textsuperscript{7,14} that investigated physical factors associated with PA used unstandardized interview-based forms of measuring PA and sporting participation. Hartman et al.\textsuperscript{7} only examined the association between 6MWT and PA, but used an unstandardized tool to measure PA. To our knowledge, Hoffman et al.\textsuperscript{13} was the only study to date with standardized measurement tools for physical function and PA to study factors associated with PA. However, this association was studied in a population of mixed childhood cancer diagnosis, which may have affected the homogeneity of the study sample and making it difficult to examine the effects of treatment and diagnosis on PA and physical function\textsuperscript{13}. Second, to our knowledge, the current study was the first to focus on understanding the physical factors influencing PA in children ages 8 – 13 years old who have completed treatment within 3 – 36 months in children. Previous studies included patients well after they have completed treatment with an median years off treatment ranging from 5.2\textsuperscript{7} – 6.3\textsuperscript{14} years, or 9.3 years after diagnosis\textsuperscript{13}, and the age of the children included in these studies varied, with studies including children ages 9.2 – 20.1 years old\textsuperscript{14}, 9.0 – 18.7 years old\textsuperscript{7}, and 9 – 18 years old with a mean age of 13.5 years\textsuperscript{13}. Third, this study also demonstrated the feasibility of performing motor performance and physical function tests as part of regular oncology follow-up visits in a hospital setting.

3.7 Study Limitations

The current study has several limitations which should be considered in interpretation of the study results. First, with a small sample size of 13 children, the study was under powered to find a significant association between our primary outcomes, and potentially allowed for type-2 errors, false negatives, to occur. The absolute effect sizes (Spearman’s rho coefficient) of non-significant associations ranged from 0.077 – 0.515, with the upper bound of this range being
considered as associations with relatively large effect sizes. Associations between PA, motor performance, and physical function, and other exploratory associations, with relatively large effects sizes may have been statistical significance if a larger sample size was included in the current study. Also, the mean measured 6MWD, 6MWD SDS, and BOT-2 SF standardized score were not statistically different by ALL risk group and anthracycline cardiotoxicity groups. Both of these group comparisons may have reached statistical significance with a larger sample size. With only 21 eligible patients identified within eight months, the participation rate (62%) was higher than anticipated, which implies it may be feasible for future studies to achieve a larger sample size.

The second limitation was participants in the current study may not be representative of all children who have completed treatment for ALL because of potential participation bias. The study may have attracted participants and parents who were more physically active and/or concerned about physical function and motor performance.

The third limitation of the current study was the cross-sectional, observational study design of the study, which did not allow for analysis involving the changes in PA, motor performance, and physical function across the time course of cancer treatment.

The fourth limitation involved the outcome measures used. The PAQ-C is a self-report PA questionnaire designed to be completed by school-aged children. Self-report PA questionnaires in children have issues with recall bias. Children tend to have greater recall accuracy for short, sporadic types of PA, which would cause overall self-report PA to be irregular, with greater recall for higher intensity PA, and lower overall recall accuracy. However, compared to objective measures of PA, such as activity monitors, self-report measurement tools are easy to administer, inexpensive, and relatively low burden to participants.
Another measurement option was a parental proxy measure, where parents and guardians estimate their child’s PA levels, but these forms of PA measurement have been reported to have poor reliability and validity\textsuperscript{122}. Furthermore, the PAQ-C only provides a final score and does not individually quantify the duration, type, intensity, and frequency of PA, making it difficult to compare with PA recommendations, guidelines and other forms of PA measurements. The PAQ-C also measures PA during school, making it difficult to capture PA during the summer and winter holidays. Finally, the PAQ-C does not have published normative references for ease of comparison. Although more expensive and difficult to manage, the use of activity monitors would allow researchers to quantify duration, intensity, type, and frequency of PA objectively.

To measure motor performance, the BOT-2 SF was useful due to its relative ease of training and administration, acceptable inter-rater, test-retest, validity (Section 2.5.2.2.1), and ability to determine a standardized score for normative reference. However, the BOT-2 SF did not allow for separate analysis of gross and fine motor scores. Also, BOT-2 SF may not be as sensitive of a measure in capturing motor impairments in childhood ALL survivors compared to the MABC-2\textsuperscript{50}. However, greater sensitivity does not imply greater accuracy in identifying motor performance impairments in this population. BOT-2 SF was designed to be a screening tool and includes purer, relatively simple, repetitive motor performance tests\textsuperscript{50}, which may be a useful clinical tool in identifying those with greater impairments. However, it may not be sensitive for early detection of motor performance impairments. The MABC-2 tests motor performance skills requiring stronger motor planning and cognitive effort\textsuperscript{50}, and it may be a useful clinical tool to distinguish fine and gross motor performance. Future studies should investigate the feasibility of using the MABC-2 and BOT-2 SF for identifying motor performance impairments in childhood ALL survivors in both research and clinical settings.
The 6MWT depends on participant motivation and interest in the task, which may have affected the results of the study\textsuperscript{52}. The current study used the ATS guidelines to administer the test in a standardized manner. Study assessments done in a hospital setting may have been associated with medical procedures routinely encountered throughout their treatment and follow-up appointments, and affected the child’s motivation and interest in performing the study assessments. The current study used the Geiger et al.\textsuperscript{114} for the normative reference data, tested children in a school setting. Although the authors attempted to prevent competition between children by testing the children in smaller groups and in several separate locations, the knowledge of peers participating in a research study can motivate competition between children and influence scores\textsuperscript{114}. Further, the Geiger study modified the standardized ATS\textsuperscript{52} script for the 6MWT, which is designed for all age groups, to help children interpret what “as far as possible” means by including “which means score as many meters as possible in 6 minutes”\textsuperscript{114} (pg. 396). Although this modification may have motivated children to walk a further distance to better reflect their physical function, comparison between studies may not be as valid. Finally, the standardized distance of the course set by the ATS is 60 m, but the current study used a pre-existing 50 m track at the British Columbia Children’s Hospital and may have affect the results of the 6MWT.

3.8 Future Studies

Future studies investigating the factors influencing PA levels in childhood ALL survivors may want to include the following considerations. The first consideration would be to use an objective measure for PA, such as pedometers or accelerometers, which may provide the potential for higher accuracy in measuring PA in youths by allowing time-resolution and more information on the intensity of the exercise bout\textsuperscript{123}. The second consideration is the measurement
tool for motor performance. Although the most suitable motor performance test to assess childhood cancer patients remains unclear, emerging evidence suggests the MABC-2 may be more sensitive in identifying motor performance impairments in childhood ALL survivors compared with the BOT-2 SF. However, research is needed to determine if the MABC-2 is detecting true motor impairments or false-positive results. The MABC-2 can provide similar ease of administration and allows for normative reference analysis for the total score like the BOT-2 SF, as well as individual analysis for motor performance tasks involving manual dexterity, aiming/catching, and balance. The third consideration would be to test the validity and reliability of a revised script for the 6MWT designed for healthy children and clinical populations of children, which may help to improve interest and motivation in children to produce results in the 6MWT truly reflective of their physical function. The fourth consideration would be to adopt a longitudinal study design to include measures starting from pre-treatment and follow children throughout and after their treatment to capture the trajectory of changes in, and associations between, PA, motor performance, and physical function.

Finally, given the lack of associations found in the current study among the measured physical outcomes and PA levels, future studies may want to explore psychosocial variables associated with PA, such as PA self-efficacy. PA self-efficacy is defined as the belief in one’s own ability to organize and perform PA, which has been shown to significantly influence PA behaviour in healthy children. A recent study conducted by Gilliam et al. investigated the extent to which self-efficacy mediated the relationship between social support and PA levels in 105 childhood cancer survivors ages 8 – 16 years old. Both self-efficacy and social support were directly associated with PA levels, and higher levels of peer and family support for PA were associated with higher levels of PA through increased self-efficacy. Other studies in childhood
cancer survivors also showed similar results, with PA levels in childhood cancer survivors being associated with PA self-efficacy\textsuperscript{61,64,77}.

3.9 Implications of Study Results

A recent large survey study investigating a large population of adult survivors of childhood ALL (n = 2648) reported survivors were more likely to be less physically active compared with the general population, and these lower levels of PA may be associated with increased risk of developing health issues, such as cardiovascular disease, obesity, osteoporosis, and all-cause mortality\textsuperscript{66}. Therefore, completion of treatment may be a suitable time to reintroduce PA to avoid the persistent low PA levels noted in ALL survivors many years after treatment\textsuperscript{9}. Previous studies have found PA levels were reduced in children actively receiving treatment\textsuperscript{70,71}. Maintenance therapy, which is final stage of treatment and suggested to be the less intensive phase of treatment, has also been considered a suitable time for PA intervention and promotion\textsuperscript{17}.

Almost all participants in the current study had lower levels of physical function compared to normative values in healthy children. Furthermore, significant differences in physical function scores were found between healthy weight children and overweight or obese children. This finding is important because pediatric\textsuperscript{17} and adult\textsuperscript{16} survivors of ALL have been reported to have higher risk of developing obesity, and associated risks for developing cardiovascular disease\textsuperscript{125}.

Based on the study findings, physical therapy programs should focus on improving physical function and weight management in children who have just completed treatment for cancer. Furthermore, despite the fact that a small percentage of participants in the current study performed below average in the motor performance tests, motor performance impairments have
been reported to be present in as many as 54% of participants in previous studies\textsuperscript{32}. Therefore, physical therapy programs should consider focusing on motor performance and skills assessment in this population. The implementation of physical function and motor performance assessments as part of follow-up appointments was shown to be feasible in the current study.

Motor performance has been associated with PA levels in healthy children\textsuperscript{49}, but the contribution of motor performance on PA in ALL survivors remains unclear. A randomized trial has been conducted by Hartman et al.\textsuperscript{38} to investigate whether an exercise program can prevent side effects of treatment (reduced bone mineral density, altered body composition, impaired motor performance, and passive ankle dorsiflexion). The study found no difference between standard care and the exercise program, and reported the null findings were due to low program adherence. Although physiotherapist-led education sessions were given parents and children regarding the side-effects of chemotherapy and the importance of exercise, parents reported the two main reasons for not adhering to program exercises were that the child was physically unable to perform daily exercise or that regular daily exercise did not seem necessary\textsuperscript{38}. However, follow-up sessions were conducted at six weeks, may have been too long for appropriate encouragement to maintain participation in the program\textsuperscript{38}.

Takken et al.\textsuperscript{92} conducted a 12-week aerobic and strength exercise training program in nine pediatric ALL survivors with an average age of 9.3 years old, who had completed treatment within 12 – 36 months. The study assessed muscle strength using a hand held dynamometer, functional mobility using the timed up-and-go, and cardiopulmonary fitness with exercise testing. Similar to Hartman et al.\textsuperscript{38}, the study only had four participants complete the intervention and found no differences in the study outcomes after completing the intervention. The authors suggested program adherence was a problem. Stages of disease, age of children, variety of
exercises, location of the intervention, and, most importantly, views and motivation of parents regarding participating in an exercise training program were key factors related to adherence. Considering these issues could potentially increase program adherence and lead to better exercise training effects from these programs.

3.10 Conclusion

In conclusion, the current study did not find an association between PA, motor performance, and physical function in children who had completed treatment for ALL. However, with a small sample size of 13 participants, the current study was not able to conclude PA in children who have completed treatment for ALL was not related to their physical function and motor performance. BMI was associated with 6MWD and 6MWD SDS, suggesting improvements in BMI status can potentially promote PA through improvements in physical function. Future studies should include a larger sample size, potentially from multiple centres to help achieve sufficient recruitment. Furthermore, a longitudinal design including baseline, objective measurements of PA at key time-points throughout and beyond treatment, may be important to enhance the understanding of the relationship between PA and physical factors in childhood ALL patients, how PA and physical factors change throughout treatment, and help to inform PA interventions during maintenance therapy and following treatment completion. Finally, including measures of psychosocial factors, such as self-efficacy, to determine the integrative impact of both physical and psychosocial factors influencing PA, may be important. The current study helped to inform the need for PA interventions in children who have completed treatment for ALL, and demonstrated the feasibility of assessing motor performance and physical function as part of oncology follow-up. These findings can be used to help improve
PA levels in childhood ALL survivors, potentially through improving the BMI status of children who have completed treatment for ALL.
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Appendices

Appendix A - Letter of Invitation

Dear Parents,

I am writing to invite you and your child to participate in a new research project we are conducting with the University of British Columbia and the British Columbia Children’s Hospital. The purpose of this pilot study is to find out what is influencing physical activity levels in children who have finished treatment for ALL. A pilot study is a small study that is done to gather important information before proposing a larger research project.

If you and your child decide to participate, we will be asking your child to fill in some questionnaires at your next visit to the Long-term Follow-up Clinic, and also ask your child to complete two assessments before or after your clinic visit. The first assessment will ask your child to perform some skills (e.g., catching or throwing a ball), and the other assessment will ask your child to walk as far as they can between two markers for six minutes. The two assessments will take about 30 minutes, and the whole study will take about 70 minutes of you and your child’s time.

If you have any questions about this study, or are interested in having your child participate in this study, please call us at [insert phone number] or by e-mail the research assistant for the study, Stanley, at [insert e-mail address].

We look forward to hearing from you. If we do not hear from you, Stanley will contact you by telephone to find out if you wish to participate in the study.

Sincerely,

Kristin Campbell, PT, PhD.  
Assistant Professor  
Dept. of Physical Therapy;  
Faculty of Medicine  
University of British Columbia

Sheila Pritchard, MBBS.  
Clinical Associate Professor  
Dept. of Pediatrics  
Faculty of Medicine  
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Stanley Hung, BPHE.  
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Dept. of Physical Therapy  
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University of British Columbia

Appendix B - Parent Consent Form

PARENTAL INFORMATION AND CONSENT FORM

Physical determinants of physical activity in children who have completed treatment for acute lymphoblastic leukemia (ALL).

Principal Investigator: Sheila Pritchard, MBBS. Clinical Associate Professor Dept. of Pediatrics, Faculty of Medicine

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Study Team Members: Anne Rankin, MScPT, MSc
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Angela Pretula, RN, MSN
Hematology, Oncology, and Bone Marrow Transplant Program at the British Columbia Children’s Hospital

Marion Nelson, RN
Hematology, Oncology, and Bone Marrow Transplant Program at the British Columbia Children’s Hospital

Stanley Hung, BPHE, Graduate Student (UBC)
Dept. of Physical Therapy, Faculty of Medicine

Consent Form – Version 4 – February 14, 2014  1 of 7
1. INVITATION
You and your child are being invited to participate in this pilot study because your child is between the age of 8-13 years, has an appointment at the Long-Term Follow-Up Clinic at the British Columbia Children’s Hospital, and has completed treatment for acute lymphoblastic leukemia (ALL) 3 to 36 months ago. A pilot study is a small study that is done to gather important information before proposing a larger research project.

2. YOUR PARTICIPATION IS VOLUNTARY
You and your child’s participation are entirely voluntary, so it is up to you and your child to decide whether or not to take part in this study. Before you and your child decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to you during the study, and the possible benefits, risks and discomforts.

If you and your child wish to participate, you will be asked to sign this consent form. A separate assent form will be provided for your child. If you do decide to take part in this study, you are still free to withdraw at any time and without giving any reasons for your decision.

If you and your child do not wish to participate, you do not have to provide any reason for your decision not to participate nor will you lose the benefit of any medical care to which you are entitled or are presently receiving.

Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

3. WHO IS CONDUCTING THE STUDY?
This study is being conducted by the University of British Columbia, Department of Physical Therapy, and by the Hematology, Oncology, and Bone Marrow Transplant Program at the British Columbia Children’s Hospital. Funding for the project is from the Start-Up funds of Dr. Kristin Campbell in the Department of Physical Therapy at UBC. Dr. Campbell and Dr. Pritchard do not receive any personal financial compensation for this study. You are entitled to request any details concerning this compensation from the principal investigators.

4. BACKGROUND
Children with, or have completed treatment for, acute lymphoblastic leukemia are not as physically active as their healthy peers, and the underlying reasons affecting their physical activity levels are not well known. The well-established physical and psychological benefits of exercise and physical activity seen in children without cancer raises health concerns for childhood cancer survivors, such as obesity, type-2 diabetes, and cardiovascular disease. These health outcomes have been suggested to be potential late effects of chemotherapy in adult survivors of ALL. However, recent studies suggest physical activity and exercise for these children is safe to do. A better understanding the factors affecting physical activity levels in childhood cancer survivors
will help inform healthcare providers promote physical activity.

5. WHAT IS THE PURPOSE OF THE STUDY?
The purpose of this study is to investigate how cancer diagnosis and treatment affects physical activity in children who have completed treatment for acute lymphoblastic leukemia, and to see what factors are related to these activities. The factors we will be looking at are movement skills and physical fitness. The results from this study will help us understand what factors affect the ability to participate in physical activity the most in children with cancer to inform physical activity promotion programs in the future.

6. WHO CAN PARTICIPATE IN THE STUDY?
Your child is eligible for this study if your child was treated at British Columbia Children's Hospital (BCCH); your child has been off treatment for acute lymphoblastic leukemia for 3 to 36 months attending the long-term follow-up clinic at the BCCH; your child is 8 to 13 years old at the time of study; you and your child is knowledgeable in English to complete the assent/consent forms, respectively; and your child knowledgeable in English to complete questionnaires.

7. WHO SHOULD NOT PARTICIPATE IN THIS STUDY?
Your child is ineligible to participate in this study if you have your child has and motor or physical impairments unrelated to the cancer diagnosis and treatment; your child has received cranial radiation; your child has had a cancer relapse; or is currently participating in other research studies that conflict with the study.

8. WHAT DOES THE STUDY INVOLVE?
If your child is eligible, and if you and your child agree to participate in the study, your child’s participation will involve filling out questionnaires during your next clinic visit at the Long-term Follow-Up Clinic, and completing two assessments during your next clinic visit. You, the parent, will not have any activities or questionnaires to complete.

The questionnaires are about how much physical activity and sports your child plays on a regular basis during the school year. Another questionnaire will also ask your child how tired he or she feels on a regular basis.

These questionnaires will take your child about 25 minutes to complete. These questionnaires will be given to you during your next clinic visit and time during your visit has been given to you to complete the questionnaires.

Your child will be completing two assessments after the appointment with your physician; one in an examination room at the Long-term Follow-Up Clinic and one in a nearby hallway. One assessment will be testing your child’s movement skills, which involves the child doing a series of physical tasks, such as catching and throwing a ball. This test will take approximately 15 minutes to complete. The second physical test is called the six-minute walk test. This will test your child’s physical fitness. The child will walk as far as he/she can around a set path in six-minutes. This test will take roughly 15
minutes to complete. Your child’s questionnaires will be completed before or after the two assessments.

The whole study will take approximately 1 – 1.5 hours of you and your child’s time.

The study will also be keeping record of your child’s height, weight, age, date of diagnosis and other medical information such as the treatment protocol used.

9. WHAT ARE MY RESPONSIBILITIES?
Prior to your scheduled appointment at the Long-Term Follow-Up Clinic at BCCH, the study staff would have contacted you about your interest in participating. If you and your child are interested in participating in the study, the study staff will arrange an appropriate time for you to complete the study tasks in conjunction with your scheduled appointment at the Long-Term Follow-Up Clinic at BCCH. We ask, to the best of your ability, to arrive at the arranged time to ensure study tasks can be completed.

At the clinic, if you and your child agree to participate, we may start the study tasks before your scheduled appointment at the Long-Term Follow-Up Clinic if time permits. If we have not started the study or have not completed all the tasks by the time of your appointment, you will be asked to stay after your appointment to complete the study.

As a parent/guardian, you will not be asked to complete any questionnaires or assessments. Also, you will be asked to not assist your child in completing the questionnaires or assessments. The study staff will help your child if any assistance is needed.

10. WHAT ARE THE POSSIBLE HARMES OR DISCOMFORTS?
The possible harms are not greater than the possible harms of everyday life. The movement skills assessment is a safe and painless test for children, and your child will not be forced to perform any tasks he or she is not comfortable doing. The six-minute walk test allows the child to exercise at a pace comfortable for him/her, and will be constantly monitored during the test and your child can stop whenever he or she wants.

11. WHAT ARE THE POTENTIAL BENEFITS OF PARTICIPATING?
The movement skills assessment can be used to see if your child has any difficulties with skills such as catching a ball or using their hands. If there are any physical problems identified during the assessments, your child will be referred to the physiotherapy department at British Columbia Children's Hospital.

12. WHAT ARE THE ALTERNATIVES TO PARTICIPATING IN THIS STUDY?
If you choose not to participate in this study or withdraw from the study, we are unaware of any comparable studies or programs offered. Not participating or withdrawing from the study will not affect your future health care in any way.
13. WHAT IF NEW INFORMATION BECOMES AVAILABLE THAT MAY AFFECT MY DECISION TO PARTICIPATE?
If any new information regarding the outcomes of the study or your child’s health becomes available or is made available during the study, you and your child will be advised of this information and you and your child can decide whether or not your wish to continue participating in the study.

14. WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE?
You and your child may decline to enter this study or withdraw from the study at any time. You do not have to provide any reason for your decision not to participate or to withdraw, and such decision will not negatively affect your future health care in any way. Dr. Pritchard may also decide to discontinue or withdraw your child from the study at any time. If you choose not to participate or withdraw from the study, all information from the study related to you and your child will be destroyed.

15. CAN I BE ASKED TO LEAVE THE STUDY?
We do not anticipate any situation where you would be asked to leave the study.

16. WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?
Your child’s confidentiality will be respected. No information disclosing your child’s identity will be released or published without your specific consent to the disclosure. However, research records and medical records identifying your child may be inspected in the presence of the Investigator, study staff, Health Canada, and the UBC Research Ethics Board for the purpose of monitoring the research. However, no records which identify your child by name or initials will be allowed to leave the Investigators’ offices.

Your child will be assigned a unique study number as a subject in this study. Only this number will be used on any research-related information collected about your child during the course of this study, so that his/her identity [i.e. your names or any other information that could identify you and your child] as a subject in this study will be kept confidential. Information containing your child’s identity will remain only with the Principal Investigator and/or study staff. The list that matches your names to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law. Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected and also gives you the right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

You and your child’s participation in this study are voluntary and you may withdraw at any time. You do not need to provide a reason for your withdrawal. The data we collect up to the point of your withdrawal from the study will be kept for data analysis purposes under strict provisions of confidentiality.
By signing this form, you do not give up any your child’s legal rights and you do not release the study investigator or other participating institutions from their legal and professional duties. There will be no costs to you for participation in this study. You will not be charged for any research procedures.

17. AFTER THE STUDY FINISHED
The results of the motor performance and physical fitness tests will be given to you after the study. If there are any physical problems identified during the assessments, your child will be referred to the Physiotherapy Department at British Columbia Children’s Hospital. A copy of the Canadian Society for Exercise Physiology (CSEP) Physical Activity Guidelines will also be provided. After the results have been processed, participants will also receive an individualized post-study letter with the participant’s individualized results showing the participants what areas of motor performance and/or physical function the participant can improve upon, as well as a resource list of community recreation activities.

18. WHAT HAPPENS IF SOMETHING GOES WRONG?
Signing this consent form in no way limits your and your child’s legal rights against the sponsor, investigators, or anyone else. In case of a serious medical event or injury as a direct result of the study, Dr. Pritchard will be informed.

19. WHAT WILL THE STUDY COST ME?
Your and your child’s participation is voluntary and you will be reimbursed $10.00 towards your parking expenses while participating in the study. You will receive this regardless of whether or not you complete the study. There will be no other additional cost associated with participating in the trial. If your child is referred for a physiotherapy assessment at BC Children’s Hospital after the assessments, there is no cost for this physiotherapy assessment.

20. WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?
If you have any questions or desire further information with respect to this study, you may contact the research assistant Stanley Hung at [Contact Information] or the study investigators, Dr. Sheila Pritchard at [Contact Information] or Dr. Kristin Campbell at [Contact Information].

21. WHO DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AND/OR EXPERIENCES AS A SUBJECT DURING THE STUDY?
If you have any concerns about your rights as a research subject and/or your experience while participating in this study, contact the Research Subject Information Line in the University of British Columbia Office of Research Services by e-mail at RSIL@ors.ubc.ca, or by phone at 604-822-8598 or toll free at 1-877-822-8598.
SUBJECT CONSENT TO PARTICIPATE

The parent(s)/guardian(s)** are satisfied that the information contained in this consent form was explained to the child** to the extent that he/she is able to understand it, that all questions have been answered, and that the child** assents to participating in the research.

- I have read and understood the subject information and consent form.
- I have had sufficient time to consider the information provided and to ask for advice if necessary.
- I have had the opportunity to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the results will only be used for scientific objectives.
- I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time without changing in any way the quality of care that I receive.
- I understand I will be reimbursed $10.00 towards parking whether or not I complete the study.
- I authorize access to my health record as described in this consent form.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- My child’s participation in this study is entirely voluntary.
- My child and I may refuse to participate or I may withdraw my child from the study at any time without jeopardy to my access to further services.
- Signing this consent form is in no way limiting my legal rights against the sponsor, investigators, or anyone else.
- I have been told I will receive a signed and dated copy of this consent form.

SIGNATURES

Printed name of subject’s Legally Acceptable Representative
Signature Date
(If applicable)

Printed name of Signature Date
Principal Investigator/designated representative

Consent Form – Version 4 – February 14, 2014 7 of 7
Appendix C - Child Assent Form

Subject Assent Form: Age 8-13yrs

A Research Study About My Physical activity

Invitation: I am being invited to be part of a research study. This research study is trying to find out why children who have cancer are playing less sports after being treated. It is up to me if I want to be in this study. No one will make me be part of the study. Even if I agree now to be part of the study, I can change my mind later. No one will be upset at me if I choose not to be part of this study.

Why are we doing this study: This study will help us learn more about why children who have finished being treated for cancer may be less physical active. I am being invited to be part of this study because 1) I am between the ages of 8 – 13 years old and 2) I have been off cancer treatment for acute lymphoblastic leukemia for three to thirty-six months (three years).

What will happen in this study?
If I agree to be in this study, the next time I go to the Children’s hospital for a visit, I will complete some question sheets about physical activity and playing sports.

For the question sheets, I will be answering some questions about how much physical activity and sports I am doing. I will also be answering questions about how tired I feel. I will be answering these questions at the hospital, and the people doing the study will help me if I have any questions. The question sheets will take 25 minutes.

At the hospital, I will also be doing two activities. For the first activity, the study helpers will ask me to do some movement skills like catching and throwing a ball. For the second activity, I will be walking between two markers for as far as I can for six minutes. These two activities will take 30 minutes.

Everything I do will take about 1-1.5 hours to finish.

Who will be doing the study?
Anne Rankin and Maria Juricic, the physiotherapists from the children’s hospital, Dr. Pritchard, and Stanley Hung, a student from the University of British Columbia, will be doing this study. They will answer any questions I have about the study. I can also call them at 604-827-1914.

Can anything bad happen to me?
The two activities I am doing are very safe. I do not have to do any of the activities if I do...
not want to. There will be people watching and helping me do the activities to make sure I will be safe. I can ask the physiotherapist and study people any questions during the two activities.

Who will know I am in the study?
Only my doctors, physiotherapist, and people who are involved in the study will know I am in it. When the study is finished, people who are involved in the study will write a report about what was learned during the study. This report will not say my name or that I was in the study. My parents and I do not have to tell anyone I am in the study if we don’t want to.

When do I have to decide?
I have as much time as I want to decide to be part of the study. I have also been asked to talk to my parents about being part of the study.

By signing this form, I do not give up any of my legal rights and the doctors, physiotherapists, and people involved in the study still have to do their medical jobs. There will be no costs to me for being part of the study.

Contact for information about the study:
If I have any questions or desire further information with respect to this study, I may contact Stanley Hung at______________

Assent:
If I put my name at the end of this form, it means that I agree to be in the study.

____________________________________
Type/Print Name of Participant

____________________________________
Signature of Participant Date

____________________________________
Name of Study Staff

____________________________________
Signature of Study Staff Date
## Appendix D - Medical Data Collection Form

**Data Collection Form**

*Study - Determinants of physical activity in children after completing treatment for acute lymphoblastic leukemia (ALL).*

Participant Study ID: ____________

<table>
<thead>
<tr>
<th>Month and Year of Birth</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Date of Treatment Completion</td>
<td></td>
</tr>
<tr>
<td>Date of Clinic Visit</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
</tr>
<tr>
<td>Total Anthracycline Dose (mg/m²)</td>
<td></td>
</tr>
</tbody>
</table>

Calculate:

<table>
<thead>
<tr>
<th>Current Age</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Time from Diagnosis to Clinic Visit</td>
<td></td>
</tr>
<tr>
<td>Time from Treatment completion to Clinic Visit</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
</tbody>
</table>

Data Collection Form – Version 2 – July 30, 2013
Appendix E - Physical Assessment Data Collection Form

Data Collection Form

**Study - Determinants of physical activity in children after completing treatment for acute lymphoblastic leukemia (ALL).**

Participant Study ID: __________

**6-Minute Walk Test**

<table>
<thead>
<tr>
<th>Tally for number of laps completed</th>
<th>Lap Distance: __________ m</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Full Laps Completed</td>
<td>__________</td>
</tr>
<tr>
<td>Partial Lap Distance: __________ m</td>
<td></td>
</tr>
<tr>
<td>Total Distance: __________ m</td>
<td></td>
</tr>
</tbody>
</table>

**BOT-2 Testing**

<table>
<thead>
<tr>
<th>Testing Date</th>
<th>Year</th>
<th>Month</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth (Y/M)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronological Age (Use birth month and year)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mobility Data Collection Form – Version 1 – September 11, 2013
Appendix F - End of Study Letter to Participants

ALL Physical Activity Study

Dear [NAME of child and family],

Thank you for participating in the ALL Physical Activity Study! The aim of the study was to look at the relationship between some of the common side effects of cancer treatment and physical activity participation. Some side effects of cancer treatment include reduced muscle strength, altered balance and coordination, and reduced heart and bone health.

For this study, your child did the 6-minute walk test and a movement test. The walking test is considered a good representation of heart health and overall physical function. The movement test assessed your child’s precise hand movements, coordination, balance, and strength. On average, children with an ALL diagnosis walk a shorter distance and may have reduced performance in movement skills compared to children without a cancer diagnosis.

The children who participated in our study, on average, also walked a shorter distance compared to children of similar age and height who have not had a cancer diagnosis. However, the children who participated in our study tended to perform at normal levels for their age on the movement test. We also did not find any relationship between the amount of physical activity the children participated in, and the 6-minute walk test or the movement test.

If you have specific questions or concerns for your child about the study results and physical activity, you may discuss this with your child’s oncologist. In that case, you are encouraged to bring a copy of this letter with you when you speak to the oncologist.

For any child, physical activity and exercise may help develop overall physical function and movement skills. If you are interested, please refer to the table on the back of this letter for a list of activities that can help with the development of particular skills related to the study assessments, and the enclosed handout of helpful websites and locations for recreation activities around your community your family can participate in.

If you have any questions about the study results, please contact us. You can reach the study coordinator, Stanley, at [hidden] or e-mail [hidden].

Sincerely,
Sheila Pritchard, BM, BS
Clinical Associate Professor
Dept. of Pediatrics
Faculty of Medicine
University of British Columbia

Kristin Campbell, PT, PhD
Assistant Professor
Dept. of Physical Therapy,
Faculty of Medicine
University of British Columbia

Stanley Hung, BPHE
Graduate Student
Dept. of Physical Therapy
Faculty of Medicine
University of British Columbia

Version 1 – April 30, 2014
ALL Physical Activity Study

The following is a list of activities categorized by what they can help your child with.

<table>
<thead>
<tr>
<th>Precise Hand Movements</th>
<th>Coordination and Balance</th>
<th>Heart Health</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Board games</td>
<td>individual Activities</td>
<td>Individual Activities</td>
<td>Individual Activities</td>
</tr>
<tr>
<td>Card games</td>
<td>Golf</td>
<td>Tag/running games</td>
<td>Skating</td>
</tr>
<tr>
<td>Frisbee</td>
<td>Yoga/Pilates</td>
<td>Running/sprinting/jogging/cross</td>
<td>Skiing/snowboarding</td>
</tr>
<tr>
<td>Individual arts and crafts (e.g. sewing, painting, beading, origami)</td>
<td>Horseback riding</td>
<td>country running</td>
<td>Weight training</td>
</tr>
<tr>
<td>Cooking/baking</td>
<td>Rock climbing (gym)</td>
<td>Bike riding</td>
<td>Rock/indoor wall climbing</td>
</tr>
<tr>
<td>Archery</td>
<td>Skateboarding</td>
<td>Skiing/snowboarding</td>
<td>Pilates/yoga</td>
</tr>
<tr>
<td>Musical instruments (piano, guitar, etc)</td>
<td>Rollerblading</td>
<td>Cross country skiing/snowshoeing</td>
<td>Body weight activities e.g. jumping, push-ups, sit-ups, lunges etc.</td>
</tr>
<tr>
<td></td>
<td>Skating Lessons</td>
<td>Jumping rope</td>
<td>Horseback riding</td>
</tr>
<tr>
<td></td>
<td>Gymnastics</td>
<td>Racquet sports (tennis, badminton)</td>
<td>Swimming (lessons)</td>
</tr>
<tr>
<td></td>
<td>Horseback riding</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hacky sack</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jumping rope</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Judo/tao chi/taekwondo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bowling</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Racquet sports (tennis, badminton)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Team Games</td>
<td>Basketball</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Volleyball</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soccer</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Team Games</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basketball</td>
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</tr>
<tr>
<td></td>
<td>Volleyball</td>
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<tr>
<td></td>
<td>Soccer</td>
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<tr>
<td></td>
<td>Team Games</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hockey</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ball activities e.g. throwing, catching</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Version 1 – April 30, 2014
Appendix G - Parking Reimbursement Form

I _____________________ have received the $10.00 parking compensation for participating in the UBC and BC Children's Hospital ALL Physical Activity Study on _____________________ (date).

Parent Signature _____________________ Date ________________