Examining Implementation of Exercise Oncology Programs

by

Joanna Frances Parkinson

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ABSTRACT

Despite the large body of evidence of the benefits of exercise for people with cancer, it is often not part of standard care. This thesis addresses two components that are relevant to the widespread implementation of exercise oncology programs in clinical practice: cost-effectiveness and symptom burden.

Paper 1: This scoping review identifies and synthesizes the literature on the use of generic utility measures used to evaluate exercise interventions for adults with any type of cancer, and identifies gaps in the current literature. Of the 2,780 citations retrieved, 10 articles were included in this review. Seven articles included economic evaluations; however, results varied considerably between studies and detailed effectiveness data derived from the generic utility measure were often not reported. To date, generic utility measures are underutilized in exercise oncology studies. Consideration should be given to the identified research evidence, population, and methodological gaps.

Paper 2: This study explored symptom burden in adults with hematological cancers participating in a community-based exercise program. It is a secondary analysis of the Alberta Cancer Exercise Hybrid Effectiveness-Implementation study, which is 12-week community-based cancer-specific exercise program. Symptom burden was measured using the revised Edmonton Symptom Assessment System. This study examined the effects of exercise on symptom burden and identified variables associated with 12-week symptom burden and change in symptom burden from baseline to 12 weeks. Three hundred fifty-four adults with hematological cancers were included in the analysis. Statistically significant improvement ($p < 0.05$) was observed for physical symptom burden, but not for total symptom burden. Baseline symptom score, program adherence, number of co-morbidities, and program type (virtual vs. in-

person) were associated with post-intervention total symptom burden. Hematological cancer type, baseline physical activity level, treatment status, sex, and employment status were associated with change in total symptom burden from baseline to 12 weeks.

Many barriers to implementing exercise in standard practice have been identified, including lack of standard referral pathways, lack of reimbursement structures for exercise, and policies directing the inclusion of exercise into standard care. Better economic evidence and evidence to support the creation of referral pathways are both necessary components to bridge the gap between research and practice, and support the implementation of exercise programs for individuals with cancer.

PREFACE

This thesis is an original work by Joanna Frances Parkinson. Chapter 2 is published in Current Oncology and is co-authored by Dr. Margaret L. McNeely, Dr. C. Allyson Jones, Paula A. Ospina, and Dr. Jeff Round. Co-authors listed have contributed to either: i.) conceptualization [J.F.P., J.R., M.L.M. and C.A.J.], ii.) methodology [J.F.P., P.A.O., J.R., M.L.M. and C.A.J.], formal analysis [J.F.P., P.A.O., J.R., M.L.M. and C.A.J.], writing—original draft preparation [J.F.P., M.L.M. and C.A.J.], writing—review and editing [all authors], supervision [M.L.M. and C.A.J.] All authors have read and agreed to the published version of the manuscript. The study in Chapter 3 received ethical approval from the Health Research Board of Alberta: Cancer Committee (HREBA.CC-23-0139).

DEDICATION

This thesis is dedicated to my amazing and inspiring mother, Shelby, and to the memory of my dear family friend, Don Smith.

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Terms and Definitions

Cancer-related terms

Cancer: an umbrella term for over 100 diseases characterized by the uncontrollable growth of abnormal cells (Canadian Cancer Society, 2023d)

Leukemia: forms in the blood stem cells and bone marrow There are several types of leukemia and they are named based on the type of cell they develop from (lymphoid stem cells or myeloid stem cells) and how quickly the tumour grows and develops. Acute leukemias begin suddenly and grow rapidly, while chronic leukemias develop and grow slowly (Canadian Cancer Society, 2023e).

Hodgkin lymphoma: begins in the lymphatic system and affects lymphocytes, which are a type of white blood cell that is found in the blood and lymph tissue (National Cancer Institute, n.d.-a). It is characterized by the presence of a specific type of abnormal cells known as Reed-Sternberg cells (Shanbhag & Ambinder, 2018)

Non-Hodgkin lymphoma: affects lymphocytes but Reed-Sternberg cells are not present (Shanbhag & Ambinder, 2018). Non-Hodgkin lymphoma be graded as indolent (low grade, slow growing) or aggressive (high grade, fast growing) (Canadian Cancer Society, 2023b).

Multiple myeloma: a cancer that forms in a type of white blood cell called a plasma cell (Canadian Cancer Society, 2023a). Multiple myeloma is characterized by an accumulation of abnormal plasma cells (called myeloma cells) in the bone marrow that crowd out the healthy blood cells (i.e. red blood cells, other white blood cells, and platelets) (Palumbo & Anderson, 2011).

Treatment-related terms

Chemotherapy: a systemic therapy involves the use of drugs to kill rapidly dividing cancer cells or stop them from dividing. The drugs cannot differentiate between cancer cells and healthy cells. Damage to healthy cells leads to side-effects such as hair loss, nausea, vomiting, and diarrhea (Canadian Cancer Society, 2023c).

Stem cell transplantation: involves replacing a patient's stem cells that have been damaged or destroyed by cancer or by high dose chemotherapy or radiation therapy used to treat cancer.

Autologous stem cell transplants use the patient's own stem cells, which are often collected before undergoing other treatments or when the patient is in remission and are stored until needed. Allogeneic stem cell transplants use stem cells from a donor, often a close relative of the patient (Canadian Cancer Society, 2023c).

Targeted therapy: uses drugs to treat cancer but these drugs target specific molecules, such as proteins, inside or on the surface of cancer cell. Targeted therapy drugs work by blocking the signals that tell cancer cells to grow and divide, thus stopping the spread of cancer cells. Since they target specific molecules, these drugs tend to be less harmful to normal cells than chemotherapy drugs, and cause fewer and less severe side effects (Canadian Cancer Society, 2023c).

Radiation therapy: therapy uses radiation to damage and destroy cancer cells. The most common type of radiation therapy is external beam which uses a machine to direct radiation to a specific part of the body (Canadian Cancer Society, 2023c)

Health economics-related terms

Cost-effectiveness analyses (CEA): Comparative analysis of the costs and outcomes (cost-effectiveness ratio) of two or more intervention alternatives with a common health outcome measured in natural units (e.g. life-years gained, disease case averted). Usually tested using a randomized controlled trial design (Rudmik & Drummond, 2013)

Cost-utility analyses (CUA): Comparative analysis of two or more different health intervention alternatives with different health outcome measures. Allows for consideration of multiple outcomes (i.e. benefit for fitness and symptoms). Effects are measured through Quality-Adjusted Life Years (QALYs) (Yousefi et al., 2016)

Quality-Adjusted Life Years (QALYs): capture the quantity and quality of life years in a single measure of health outcome (Torrance, 1986). The individual's health is assessed using a preference-based quality of life measure; and the value is converted into a health utility value (i.e. a common currency). Calculation of QALY = an individual's utility values are multiplied by the time that is spent in specific health state (i.e. length of time or life years saved that is adjusted for any loss in quality of life) (Rudmik & Drummond, 2013).

Health utility: a measure to reveal preferences for a given health state that range from 0 (death) to 1 (full health) (Yousefi et al., 2016).

Generic utility measure: health-related quality-of-life instruments that are used as an indirect method of estimating utility values for computing QALYS. Commonly used generic utility measures include the EuroQol (EQ-5D), Short Form (SF-6D), and the Health Utilities Index (HUI) (Yousefi et al., 2016).

Incremental cost-effectiveness ratio (ICER): the ratio of the difference in cost between interventions (e.g., exercise versus control) and the difference in benefit between the two interventions. Interventions that show improved benefit and are less costly are more likely to be implemented (Rudmik & Drummond, 2013).

Health-related quality of life (HRQL): a complex and multidimensional concept that is only one component of the overall paradigm of quality of life (Patrick & Erickson, 1993). It represents domains that are directly related to the health of a person including symptoms, mental health, physical functioning, role functioning, and an overall perception of health (Wilson & Kaplan, 1995).

Symptom-related terms

Symptoms: Effects of disease and treatment that are observed by the person experiencing them and measured through self-report (Cleeland, 2007)

Symptom burden: a summative indicator of the severity and impact of multiple symptoms experienced by a patient and is an important measure of the impact of cancer and its treatment on survivors (Cleeland, 2007).

Acute symptoms: Cancer and treatment related symptoms resolve relatively quickly after treatment (Gegechkori et al., 2017).

Chronic symptom: Caner and treatment related symptoms that are long-term, sometimes lasting for years after treatment is completed (Gegechkori et al., 2017).

Late-presenting effects: Effects that are not present at the time of cancer treatment that develop months or years after treatment completion (Gegechkori et al., 2017).

Study-related terms

Alberta Cancer Exercise (ACE) program: a hybrid effectiveness-implementation study evaluating a community group-based exercise program for individuals with a diagnosis of any type of cancer (McNeely et al., 2019)

Edmonton Symptom Assessment System revised (ESAS-r): a self-report tool used to measure an individual's symptom burden that includes nine symptoms: pain, tiredness, drowsiness, nausea, lack of appetite, shortness of breath, depression, anxiety, and overall well-being (Hui & Bruera, 2017).

CHAPTER 1: INTRODUCTION AND BACKGROUND INFORMATION

The incidence of cancer each year in Canada has been rising, primarily due to Canada's aging and growing population (Brenner et al., 2022). It is estimated there were 239,100 new cancer diagnoses in 2023 (Canadian Cancer Society Advisory Committee, 2023), a substantial increase from approximately 137,695 in 2000 (Statistics Canada, 2022). Despite the increase in diagnoses, advances in both early detection and treatments have led to substantial improvements in survival rates for many cancers (Canadian Cancer Society Advisory Committee, 2023).

Consequently, there is a large population of individuals with cancer, many of whom experience physical and psychological symptoms and side-effects caused by the disease and its treatment, with a lasting impact on their overall quality of life (Harrington et al., 2010). There is an urgent need to expand the focus of oncology research beyond merely treating the disease to managing symptoms and optimizing survivors' quality of life during and after treatment.

Symptom Burden

Symptoms are observed by the person experiencing them and can only be measured through self-report (Cleeland, 2007). Symptoms that arise during cancer treatment can be acute, meaning they resolve relatively quickly after treatment, or long-term, sometimes lasting for years after treatment is completed (Gegechkori et al., 2017). Late effects are effects not present at the time of cancer treatment that develop months or years after treatment completion (Gegechkori et al., 2017). Symptoms can be assessed individually or multiple symptoms can be assessed as a summary score, known as symptom burden. Symptom burden is a summative indicator of the severity and impact of multiple symptoms experienced by a patient and is an important measure of the impact of cancer and its treatment on survivors (Cleeland, 2007). Cancer-related symptoms can vary based on type of cancer, treatments received, and individual patient factors.

Some of the most common cancer-related symptoms include fatigue, pain, nausea, and trouble concentrating (National Cancer Institute, n.d.-b).

Hematological Cancers

Hematological cancers, also called blood cancers, begin in blood-forming tissues such as the bone marrow and cells in the immune system (National Cancer Institute, n.d.-a). Common types include leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma. Combined, hematologic cancers were projected to account for 9.3% of new diagnoses in Canada in 2023, slightly behind colorectal cancer (10.1%) and prostate cancer (10.8%; (Canadian Cancer Society Advisory Committee, 2023). The largest increases in 5-year net survival for all cancers since the early 1990s have been for hematological cancers, primarily related to advancements in cancer treatments, early detection, and supportive care (Canadian Cancer Society Advisory Committee, 2023).

Symptom Burden in Hematological Cancers

Two studies involving people with multiple myeloma found that females and those over 65 years of age had higher symptom burden than males and younger patients (Campagnaro et al., 2008; Kamal et al., 2021). In a cross-sectional study of individuals with various leukemias, lymphomas, and multiple myeloma, the mean number of symptoms reported was significantly ($p < 0.05$) greater for those on treatment, those with poorer performance status, inpatients, and those with advanced disease (Manitta et al., 2011). A large cohort study in The Netherlands reported significantly more fatigue, dyspnea, appetite loss, and pain in acute myelogenous leukemia survivors than in the general population ($p < 0.05$). They also found that individuals who received stem cell transplants had more fatigue and dyspnea than those who did not receive stem cell

transplants. As well, longer time since diagnosis was significantly associated with less nausea, vomiting, and diarrhea (Leunis et al., 2014).

A cross-sectional American study of 3,392 people with cancer found higher odds of severe symptoms in people who were under 55 (odds ratio (OR) 2.31; 95% confidence interval (CI) 1.91-2.80), had an annual household income under $40,000 (OR 1.61; 95% CI 1.34-1.94), were currently unemployed (OR 1.27; 95% CI 1.05-1.53), had no more than a high school education (OR 1.29; 95% CI 1.09-1.53), or were uninsured/underinsured (i.e., on Medicaid or medical assistance; OR 1.57; 95% CI 1.10-2.24) (Shi et al., 2011). Clinical characteristics associated with higher odds of severe symptoms included having lung cancer (OR 2.27; 95% CI 1.76-2.94), having distant metastases (OR 2.05; 95% CI 1.60-2.62), actively receiving chemotherapy (OR 1.93: 95% CI 1.47-2.52) and having two or more comorbidities (OR 3.22; 95% CI 2.65-3.91). However, the majority of individuals in this study had either breast (24%), prostate (18%), or colorectal (15%) cancer and only 6% had hematological cancer (Shi et al., 2011).

Multivariable logistic regression analysis of Edmonton Symptom Assessment System revised version (ESAS-r) data from the Ontario Cancer Registry (n = 120,745) showed that individuals with hematological cancers within the first year after diagnosis had significantly increased odds of reporting moderate to severe scores for eight ESAS-r symptoms when compared with individuals with breast cancer. Anxiety was the only symptom that was not significant (OR 1.05; 95% CI 1.00-1.11) (Bubis et al., 2018). For the symptoms that were significantly greater in the hematological cancer group, odds ratios ranged from 1.17 (95% CI 1.10-1.23) for depression to 2.00 (95% CI 1.87-2.15) for nausea. The same study found that female sex, younger age (<50), higher number of comorbid conditions, and lower income were

all associated with significantly higher odds of moderate-to-severe scores for multiple symptoms in individuals across various cancer types (Bubis et al., 2018).

Exercise in Hematological Cancers

Since 2019, several systematic reviews have been published on the effects of exercise in adults with hematological cancers (Abo et al., 2021; Knips et al., 2019; Xu et al., 2022). There is considerable variability in exercise parameters of interventions in the literature and also in study outcomes. Studies usually include a combination of fitness outcomes and patient-reported outcomes but the chosen measures vary from study to study. This section summarizes the literature for the effects of exercise on quality of life and symptom outcomes.

A systematic review by Abo et al. (2021), which also included a meta-analysis, examined the effects of exercise on people with hematological cancers treated with bone marrow transplantation. Twenty-four randomized controlled trials (RCTs) and three nonrandomized trials were included (n=2,432) in the review. Interventions took place prior to transplantation, during hospital stay, and following discharge post transplantation (Abo et al., 2021). Pooled data from 11 of the included studies showed evidence of a statistically significant improvement (mean difference =3.38 points; 95% CI = 0.37 to 6.39; p =0.03) with exercise compared to control for global health-related quality of life (HRQL) measured using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ-C30) (Aaronson et al., 1993). For the fatigue subscale of the EORTC-QLQ-C30, pooled data from eight studies showed a statistically significant improvement (mean difference= 2.52; 95% CI 0.42 to 4.63; p =0.02). No significant differences (p >0.05) were found for pain, dyspnea, or diarrhea (Abo, 2021).

A more recent systematic review by Xu and colleagues (2022) investigated the effects of exercise in hematological cancer patients who did not receive stem cell or bone marrow transplant. Fifteen studies with 874 participants were included. No significant differences ($p > 0.05$) between exercise and usual care groups were found for fatigue nor quality of life. Sub-group analysis found that quality of life significantly improved (standardized mean difference [SMD] 0.44; 95% CI=0.08 to 0.8; $p = 0.02$) in the intervention group following combined aerobic and resistance interventions but no significant difference ($p > 0.05$) was found when interventions involved aerobic exercise alone (Xu 2022).

Another systematic review and meta-analysis (Knips 2019), which included 18 aerobic exercise RCTs for adults with various hematological cancers (n=1892) found no evidence that aerobic exercise improved quality of life (SMD 0.11; 95% CI -0.03 to 0.24; $p = 0.14$) or anxiety (SMD 0.03; 95% CI -0.3-0.36; $p = 0.85$). There was evidence that aerobic exercise had a small effect on depression (SMD 0.19; 95% CI 0.0-0.38; $p = 0.05$) and a small-to-moderate effect on fatigue (SMD 0.31; 95% CI 0.13-0.48; $p = 0.0005$). Subgroup analysis comparing studies that included individuals undergoing stem cell transplant versus those that were not, found that exercise improved fatigue significantly in the stem cell transplant group (SMD 0.31; 95% CI 0.12-0.51; $p < 0.0001$). No significant differences were found in the subgroup of studies not involving stem cell transplant (SMD 0.3; 95% CI -0.09-0.69: $p = 0.13$) despite a similar SMD to the transplant group. This lack of significant difference may be due to the smaller sample size in the no transplant group (n=242, four studies) compared to the transplant group (n=584, five studies). For quality of life, a slight improvement was found in the no stem cell transplant group (SMD 0.26; 95% CI 0-0.53; $p = 0.05$) but no improvement was found in the stem cell transplant group (SMD 0.13; 95% CI -0.07-0.33; $p = 0.22$).

Most of the research in exercise for individuals with hematological cancers has examined individual symptoms scores rather than summary scores of symptom burden. Measures of symptom burden provide a more comprehensive description of the impact of cancer and its treatment than measures of individual symptoms (Burkett & Cleeland, 2007). The summative effect of multiple symptoms may be more meaningful to the individual with cancer than the effect on a single symptom; therefore symptom burden is an outcome worth investigating (Cleeland & Reyes-Gibby, 2002).

With the increases in survival of many hematological cancers in recent decades, there is a need for more research examining how best to manage both cancer-related, and treatment-related symptoms in this patient population. While there is evidence demonstrating benefit from exercise for individual symptoms (Abo et al., 2021; Knips et al., 2019; Xu et al., 2022), little is known about the effects of exercise on symptom burden in individuals with hematological cancers. Furthermore, little is known about the variables (socio-demographic, behavioural, and medical) that may be associated with symptom burden, and/or may predict response to exercise in the hematological cancer population.

Cost-effectiveness in Healthcare Interventions

HRQL is commonly used to assess cost-effectiveness in healthcare interventions. HRQL is a complex and multidimensional concept that is only one component of the overall paradigm of quality of life (Patrick & Erickson, 1993). It represents domains that are directly related to the health of a person including symptoms, mental health, physical functioning, role functioning, and an overall perception of health (Wilson & Kaplan, 1995). Measuring HRQL is useful for evaluating the impact of disease and/or treatment on patients, assessing health-related gaps across sub-populations, and measuring and comparing the effectiveness of various healthcare

interventions (Wells et al., 2011). There are many standardized measures for measuring HRQL, both generic and condition specific. Generic HRQL measures provide a multi-dimensional construct, permit comparisons with other patient populations, and facilitate economic evaluations.

Economic evaluations are an important component needed for implementation because policy and decision-makers must make decisions regarding the allocation of scarce healthcare resources (Goodacre & McCabe, 2002). Cost-effectiveness evaluations of healthcare interventions compare the resources consumed (costs) with the health improvement created by the intervention. Health improvement can be measured in a variety of ways. A common measurement method for economic evaluations are health state utility scores which are values that are assigned to a health state on a scale anchored at 1.0 being a state of perfect health and 0 representing a health state equivalent to death (Torrance, 1986). Health utility scores reflect the desirability of a given health condition (Lenert & Kaplan, 2000). Utility scores can be used to calculate Quality Adjusted Life Years (QALYs) which combine increases in quality of life (measured using utility scores) with the time spent in improved health states. Using generic utility measures to calculate QALYs for economic evaluations allows for comparison across different patient populations (Goodacre & McCabe, 2002). When QALYs are used as the measure of effect in an economic evaluation it is called a cost-utility analysis (CUA) (Torrance, 1986). The additional cost per QALY gained when comparing an intervention to a control or usual care, which is known as the incremental cost-effectiveness ratio (ICER), is often calculated and used to guide decisions about what interventions should be funded (Edlin et al., 2015).

Generic utility measures have been used to assess HRQL and cost-effectiveness in cancer populations (Bremner et al., 2007; Paracha et al., 2016; Peasgood et al., 2010), but it is unknown how often these measures are used in exercise oncology studies.

Problem Statement and Purpose of the Thesis

Research has demonstrated that exercise is safe and beneficial for most people with cancer (Campbell et al., 2019; Stout et al., 2017). Interventional studies demonstrate that exercise programs can improve physical functioning, psychosocial well-being, and quality of life in people with cancer (Stout et al., 2017). Although evidence supports the benefits of exercise in oncology (Campbell et al., 2019; Stout et al., 2017), exercise is not often part of standard cancer care. There is a need to move exercise oncology research from a focus on efficacy to determining how to best implement exercise programs into standard care.

This thesis addresses two components that are relevant to the widespread implementation of exercise oncology programs in clinical practice: cost-effectiveness and symptom burden. Paper one (chapter 2) is a scoping review of the use of generic utility measures in exercise oncology research. This paper explores findings related to utility measures in exercise oncology research, identifies research gaps, and makes recommendations for future studies to better facilitate economic evaluations. Paper two (chapter 3) of this thesis explores symptom burden in adults with hematological cancer participating in a community-based exercise program. This paper evaluates the effectiveness of the exercise program on symptom burden and the variables associated with post-intervention symptom burden.

Thesis Objectives

Scoping Review (Chapter 2)

1) To explore the type, frequency, and findings related to the use of utility measures in exercise oncology research.

2) To describe the study designs, characteristics of adult cancer populations, exercise prescription factors, and timing of the exercise interventions in the cancer trajectory.

3) To identify potential research gaps in the current literature.

Symptom Burden Analysis (Chapter 3)

1) To examine the effectiveness of a cancer-specific 12-week exercise program on self-reported total and physical symptom burden as measured by ESAS-r in adults with hematological cancers.

2) To identify the baseline socio-demographic, behavioural, and medical variables associated with 12-week ESAS-r total symptom score and change in total symptom burden score from baseline to 12 weeks.

CHAPTER 2: GENERIC HEALTH UTILITY MEASURES IN EXERCISE ONCOLOGY: A SCOPING REVIEW AND FUTURE DIRECTIONS

Published in Current Oncology

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Abstract

Despite the evidence that exercise is effective at mitigating common side effects in adults with cancer, it is rarely part of usual cancer care. One reason for this is the lack of economic evidence supporting the benefit of exercise. Economic evaluations often rely on the use of generic utility measures to assess cost effectiveness. This review identifies and synthesizes the literature on the use of generic utility measures used to evaluate exercise interventions for adults with cancer. A systematic search of the literature from January 2000 to February 2023 was conducted using four databases (Medline, EMBASE, CINAHL, Academic Search Complete). Exercise studies involving adults with any type of cancer that used a generic utility measure were eligible for inclusion. Of the 2780 citations retrieved, 10 articles were included in this review. Seven articles included economic evaluations, with varying results. Four studies reported on cost-effectiveness; however, detailed effectiveness data derived from the generic utility measure were often not reported. Generic utility measures help to compare baseline values of and changes in health utility weights across studies and to general population norms; however, to date, they are underutilized in exercise oncology studies. Consideration should be given to the identified research evidence, population, and methodological gaps.

Introduction

Exercise is an evidence-based strategy to address many of the negative effects of cancer treatment, including fatigue, depression, and anxiety (Campbell et al., 2019; Cormie et al., 2017; Stout et al., 2017). Systematic reviews and meta-analyses show favourable effects of exercise on HRQL, according to cancer-specific measures such as the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) (Aaronson et al., 1993) and the Functional Assessment of Cancer Therapy (FACT) (Cella et al., 1993). Significant improvements have been found with exercise compared to control for overall HRQL (Buffart et al., 2017; Fukushima et al., 2021; Gerritsen & Vincent, 2016; Mishra et al., 2012; Sweegers et al., 2018) and specific domains including physical functioning (Buffart et al., 2017; Fukushima et al., 2021; Mishra et al., 2012; Sweegers et al., 2018), role functioning (Fukushima et al., 2021; Mishra et al., 2012), emotional functioning (Fukushima et al., 2021), and social functioning (Mishra et al., 2012). Despite many benefits, exercise programs are often not a part of standard cancer care. Given the benefits and relatively low costs of implementing exercise programs, there is a need to move exercise oncology research from a focus on efficacy to effectiveness—meaning determining how to best implement exercise programs within standard care. Economic evaluations provide necessary information for implementation, as policy and decision-makers often must make decisions regarding how to best allocate scarce healthcare resources (Goodacre & McCabe, 2002). Cost-effectiveness analyses (CEAs) of healthcare interventions compare the resources consumed (costs) with the health changes (consequences) resulting from the intervention (See Table 1: key terms) (Rudmik & Drummond, 2013). To best inform resource decisions, equitable comparisons across different healthcare systems are needed. Quality-adjusted life years (QALYs) is a commonly used summary measure for economic evaluations of healthcare (Yousefi et al., 2016). It includes the concept of duration and health-related quality of

life and is the product of the duration of time spent in a certain health state and the utility score (HRQL weight). It is expressed as a single index, which permits comparisons across different populations and conditions (Goodacre & McCabe, 2002). For instance, a QALY measurement can be obtained with an exercise program (treatment) compared with no treatment. When QALYs are the outcome of an economic evaluation, it is referred to as a cost–utility analysis (CUA) (Torrance, 1986).

Table 2.1 Economic Evaluations: Key Terms

Term	**Definition**
Health economic evaluation	Investigation of the value for money of different health interventions. Information is used to inform a recommendation for adoption of a new treatment into routine practice. There are four main types of health economic evaluations: (i) cost-minimization, (ii) cost-effectiveness analyses, (iii) cost-utility analyses, and (iv) cost-benefit analyses (Goodacre & McCabe, 2002).
i. Cost-minimization	This analysis is used when the outcome or benefit of the intervention is the same, and the costs are simply compared (Goodacre & McCabe, 2002).
ii. Cost-effectiveness analyses (CEA)	Comparative analysis of the costs and outcomes (cost-effectiveness ratio) of two or more intervention alternatives with a common health outcome measured in natural units (i.e. life-years gained, disease case averted). Usually tested using a randomized controlled trial design (Rudmik & Drummond, 2013).
iii. Cost-utility analyses (CUA)	Comparative analysis of two or more different health intervention alternatives with different health outcome measures. Allows for consideration of multiple outcomes (i.e. benefit for fitness and symptoms). Effects are measured through Quality-Adjusted Life Years (QALYs) (Yousefi et al., 2016).
iv. Cost-benefit analyses	A complex form of analysis that compares the costs of two or more intervention alternatives in terms of their relative benefit on direct, indirect and intangible costs that are based on preferences of those affected (willingness to pay or loss/ gain in income due to illness) (Yousefi et al., 2016).

Time horizon	Period over which health outcomes/ effect data and costs are collected (Torrance, 1986).
Quality-Adjusted Life Years (QALYs)	QALYs capture the quantity and quality of life years in a single measure of health outcome (Torrance, 1986). The individual's health is assessed using a preference-based quality of life measure; and the value is converted into a health utility value (i.e. a common currency). Calculation of QALY = an individual's utility values are multiplied by the time that is spent in specific health state (i.e. length of time or life years saved that is adjusted for any loss in quality of life) (Rudmik & Drummond, 2013).
Utility	Utility is a measure to reveal preferences for a given health state that range from 0 (death) to 1 (full health) (Yousefi et al., 2016).
Time trade off method	A direct method of determining the health utility state where the choice is between living the rest of life in an impaired state, or living in full health for a shorter period of time (Whitehead & Ali, 2010).
Standard gamble methods	A direct method of determining the health utility state where the choice is between the certainty of remaining in a particular health state, or taking a gamble of either being in full health or risking death. The probability of experiencing death is varied until the individual is indifferent between the certainty and the gamble (Whitehead & Ali, 2010).
Generic utility measure	Generic utility measures are health-related quality-of-life instruments that are used as an indirect method of estimating utility values for computing QALYS. Commonly used generic utility measures include the EuroQol (EQ-5D), Short Form (SF-6D), and the Health Utilities Index (HUI) (Yousefi et al., 2016). Valuation methods used may include the time trade-off (i.e., EQ-5D) and standard gamble methods (i.e., SF-6D and HUI).
Incremental cost-effectiveness ratio (ICER)	The ratio of the difference in cost between interventions (e.g., exercise versus control) and the difference in benefit between the two interventions. Interventions that show improved benefit and are less costly are more likely to be implemented (Rudmik & Drummond, 2013).

Utilities are needed to generate a QALY measurement value. Utilities are preference weights which are measured using a cardinal scale of 0–1, using anchors of 0 equivalent to being dead and 1 equivalent to full heath (Torrance, 1986). Negative values represent states 'worse than death'. The measurement of health utilities can be obtained by either direct or indirect elicitation methods (Whitehead & Ali, 2010). Methods of valuing HRQL weights using direct elicitation commonly include visual analogue scale (VAS), standard gamble (SG), or time trade-off methods (TTO) (National Institute for Health and Care Excellence, 2013); however, this type of method can be challenging for participants and is very time consuming. Indirect elicitation methods use a generic utility measure, which includes a health status classification system with pre-defined preference weights assigned to each health state (Rudmik & Drummond, 2013). Generic utility measures often include peripheral dimensions of health that are not central to the specific condition, which in this case is cancer. A range of generic measures exist with differing dimensions, levels for each dimension, and populations used as a base for the preferences. The valuation methods to derive the preferences also differ. For instance, the EQ-5D uses a TTO whereas the Health Utilities Index (HUI) and SF-6D use SG methods (Canadian Agency for Drugs and Technologies in Health, 2017; Paracha et al., 2016).

When comparing an intervention with a control or comparison intervention, an economic value can be derived using a CUA. The incremental cost-effectiveness ratio (ICER) is the ratio of the difference in cost between the intervention and comparison and the difference in effectiveness between the two groups. It summarizes the cost per unit of health benefit gained and can guide funding decisions regarding interventions (Rudmik & Drummond, 2013). Guidelines for economic evaluations from both the National Institute for Health and Care Excellence in the United Kingdom (National Institute for Health and Care Excellence, 2013) and

the Canadian Agency of Drug and Technologies in Health (Canadian Agency for Drugs and Technologies in Health, 2017) recommend the use of generic health utility measures for economic evaluation of healthcare interventions.

Generic utility measures have been used in cancer populations (Bremner et al., 2007; Paracha et al., 2016; Peasgood et al., 2010), but it is unknown how often these measures are used in exercise oncology studies. The purpose of this scoping review is to identify and synthesize the literature on generic utility measures used to evaluate exercise interventions for adults with cancer. Specific objectives are (1) to explore the type, frequency, and findings related to the use of utility measures in exercise oncology research; (2) to describe the study designs, characteristics of adult cancer populations, exercise prescription factors, and timing of the exercise interventions in the cancer trajectory; and (3) to identify potential research gaps in the current literature.

Materials and Methods

A scoping review based on the framework proposed by Arksey and O'Malley (Arksey & O'Malley, 2005) and refined by Levac and colleagues (Levac et al., 2010) was performed to address the objectives. We also followed the PRISMA Extension for Scoping Reviews (PRISMA-ScR) (Tricco et al., 2018). A scoping review was selected rather than a systematic review as our interest was in exploring the characteristics of studies and identifying research gaps rather than providing evidence to inform clinical practice or policy (Munn et al., 2018; Peters et al., 2015). The protocol for this review was registered on Figshare (https://figshare.com/articles/preprint/Generic_Health_Utility_Measures_in_Exercise_and_Cancer_Scoping_Review_Protocol/17868740 (accessed on 4 January 2022)).

Stage 1: Identifying the Research Question

Our research questions are as follows: What is the current state of the exercise oncology research using generic utility measures in adults during and after cancer treatment? Specifically, we want to know what patient populations are included, which exercise intervention parameters are prescribed, and what health utility measures are used? Furthermore, what specific metrics are reported, what are the baseline utility values, and what are the changes in utility scores? For this review, we defined exercise as "planned, structured, and repetitive bodily movement performed to improve or maintain one or more components of physical fitness" (Caspersen et al., 1985).

Stage 2: Identifying Relevant Studies

A health sciences librarian in conjunction with the research team developed search strategies for four electronic databases (Medline, Embase, CINAHL, and Academic Search Complete). Articles were limited to the English language and were published between January 2000 and February 2023. We limited the search to 2000 onwards to reflect the most current research available given advances in oncologic treatments and improved overall cancer survival (Canadian Cancer Society Advisory Committee, 2023). Study eligibility included (1) adults (18+ years) with any type of cancer diagnosis, (2) structured physical exercise intervention that targeted multiple muscle groups and one or more health related components of physical fitness (cardiorespiratory endurance, muscular endurance, muscular strength, body composition, and flexibility) and was implemented by a qualified exercise or rehabilitation professional, (3) delivered in a group or individual format during or after cancer treatment, (4) randomized controlled trials, intervention studies, comparative studies, follow-up studies, or economic evaluations of any of the aforementioned study designs, (5) a minimum of 20 participants in the intervention group, and (6) any version of a generic utility measure as a primary or secondary outcome including EQ-5D, the Short-Form Six-Dimension (SF-6D), the Health Utilities Index

Mark 2 (HUI2) and Mark 3 (HUI3), Assessment of Quality of Life (AQoL), Quality of Well-Being (QWB), and 15D©. Studies were excluded if they were recreational activities such as yoga, dance, Pilates, tai-chi, qigong, or sport-based. Multimodal interventions, such as combined exercise and nutrition, were excluded. Interventions that included additional non-exercise therapeutic modalities such as ultrasound were also excluded. Articles were excluded if the study sample included children, adolescents, or adult survivors of childhood cancer.

Stage 3: Study Selection

Citations were uploaded to Covidence systematic review software version 2.0 (Veritas Health Innovation, Melbourne, VIC, Australia) for citation management and the screening process. Duplicate citations were identified and removed. Two reviewers (JFP and PAO) independently screened the titles and abstracts. "Strong" (McHugh, 2012) inter-rater reliability (kappa = 0.9) between the 2 reviewers was reported for the first 50 citations. Disagreement between reviewers was resolved through discussion, and when necessary, through third party adjudication (CAJ, MLM). Both reviewers then independently screened half of the remaining citations. Two reviewers (JFP and PAO) independently screened the first 10 full texts with "perfect" (McHugh, 2012) inter-rater reliability (kappa = 1.0) before each screened half of the remaining articles.

Stage 4: Charting the Data

Data were extracted from the full texts of the included studies. A standardized form was used to collect data on the study characteristics (author, publication year, country of publication, study design), study population characteristics (participant demographic and medical characteristics, sample size), intervention and comparators (e.g., description, duration of treatment, adherence, losses to follow-up), outcome measures, type of economic evaluation, and

results. Extraction data were downloaded to Microsoft Excel for review. One author (JFP) extracted the data and two other authors (PAO, MLM) checked the data to ensure accuracy. When necessary, previous trial publications, including protocols, were accessed to extract further details about the intervention and participants.

Stage 5: Collating, Summarizing, and Reporting Results

To provide a broad overview of the included studies, we summarized and collated data on the cancer type, participant characteristics, exercise intervention details (frequency, intensity, type of exercise, length of session, duration of intervention), whether the intervention took place during or after cancer treatment, and the generic utility measures used, rationale for inclusion of the measure(s), and findings related to use of these measures including utility scores, QALYs, and ICERs.

Results

The search yielded 4136 citations of which 1356 duplicates were removed, and the remaining 2780 (67%) citations were reviewed for eligibility. In total, 223 articles were included in the full-text screen, of which 10 articles with a total of 1285 adults with cancer were included in the review. During full-text screening, the most common reason for study exclusion was not including a generic utility measure as an outcome (Figure 2.1).

Study Characteristics

The majority (60%) of the included studies were from Europe (Netherlands (Kampshoff et al., 2018; May et al., 2017; van Dongen et al., 2019; van Waart et al., 2018); Spain (Cuesta-Vargas et al., 2014; Rosero et al., 2020). Three studies were from Australia (Edmunds et al., 2020; Gordon et al., 2017; Haines et al., 2010) and one was from Japan (Ochi et al., 2022). All included articles were published between 2010 and 2023 and included data collected between

2006 and 2020 (Table 2.1). Seven studies included a CUA examining incremental cost per QALY gained and included a generic utility measure to calculate QALYs (Edmunds et al., 2020; Gordon et al., 2017; Haines et al., 2010; Kampshoff et al., 2018; May et al., 2017; van Dongen et al., 2019; van Waart et al., 2018). Three studies included a generic utility measure but did not report a CUA, including one RCT from Japan (Ochi et al., 2022), and two non-randomized studies from Spain (Cuesta-Vargas et al., 2014; Rosero et al., 2020).

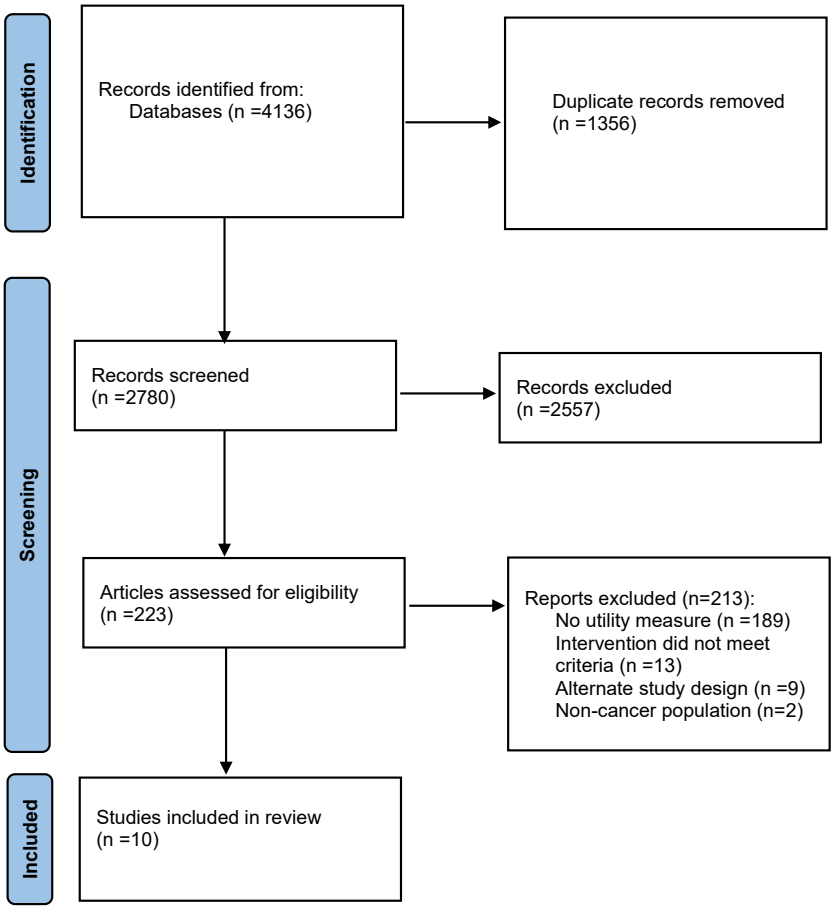

Figure 2.1 PRISMA flow diagram

Participants

Overall, 72% (n = 913) of participants in the ten included studies were individuals with breast cancer, with the majority of participants across studies being female (80%). The mean age reported in the 10 studies ranged from 48 to 76.2 years. Five studies were specific to breast

cancer (Cuesta-Vargas et al., 2014; Gordon et al., 2017; Haines et al., 2010; Ochi et al., 2022; van Waart et al., 2018). A large RCT study included 204 individuals wit h breast and 29 with colon cancer; however, the colon subset was relatively small (n=14 in the intervention and n=15 in the control) (May et al., 2017). Another RCT study of 277 participants included those diagnosed with breast cancer (n=181), colon cancer (n=49), lymphomas (n=26), ovarian (n=12), testis (n=5), and cervix cancer (n=4) (Kampshoff et al., 2018). The remaining three studies were specific to prostate cancer (n=100) (Edmunds et al., 2020), lung cancer (n=34) (Rosero et al., 2020), and hematological cancers (n=109) (van Dongen et al., 2019).

Exercise Interventions

All of the exercise interventions included combined aerobic and resistance exercise training, with four taking place during cancer treatment (Haines et al., 2010; May et al., 2017; Rosero et al., 2020; van Waart et al., 2018) and five after treatment (Cuesta-Vargas et al., 2014; Edmunds et al., 2020; Kampshoff et al., 2018; Ochi et al., 2022; van Dongen et al., 2019). One intervention took place after breast cancer surgery, with the majority of participants receiving at least one type of treatment (chemotherapy, radiotherapy, and/or hormone therapy) during the intervention, but being on treatment was not a requirement to participate (Gordon et al., 2017). All exercise sessions were 45 to 60 min in length, occurring from one to three times a week over 8-week to 8-month periods. Two interventions were home-based, with one using an app to deliver the intervention (Ochi et al., 2022) and one providing participants with a DVD of the exercises (Haines et al., 2010). One intervention included both in-person and independent home-based exercise sessions (Gordon et al., 2017). The remaining seven interventions were fully in-person. Details of participants and interventions can be found in Table 2.2.

Table 2.2. Participant and intervention details

Study/country	Cancer type N (%)	Groups	Mean Age (SD)	Sex n (%)	Timepoint** and duration of exercise intervention	Exercise prescription parameters				Control or comparison intervention
						Type	Intensity	Frequency/ Duration	Setting	
Gordon et al. 2017 Australia	Breast 194 (100)	Full study: Face to face intervention: 67 Telephone intervention: 67 Control- 60 Included in CUA: Intervention- 134, Control- 60	Face to face- 51.2(8.8) Telephone- 52.2 (8.6) Control- 53.9 (7.7)	194 (100) female	After surgery. During the trial, 69% of women underwent chemotherapy, 71% underwent radiotherapy, and 64% began hormone therapy. 8 months	Aerobic interval and muscular strength training	Moderate	Supervised sessions weekly for months 1-2, biweekly for months 3-4, monthly for months 5-8. Unsupervised sessions were 2-4 times per week	Unsupervised and telephone sessions were home-based, supervised sessions for in-person group were clinic-based	Usual care
van Waart et al. 2018 The Netherlands	Breast 153 (100)	Intervention: 76 Control: 77	Intervention: 49.9 (8.4) Control: 51.6 (8.8)	Intervention: 2 (3) male, 74 (97) female Control: 77 (100) female	During treatment Varied- each participant exercised for the duration of their chemotherapy regimen Intervention group participants had mean of 110.8 (SD = 28.6) chemotherapy days	Aerobic and resistance training	Moderate to high	50 min sessions 2x/week	Clinic-based, supervised	Usual care
Haines et al. 2010 Australia	Breast 89 (100)	Intervention: 46 Control: 43	Intervention: 55.9 (10.5) Control: 54.2 (11.5)	89 (100) female	During treatment 6 months	Strength, balance, shoulder mobility and cardiovascular endurance program	Moderate	NR	Home-based unsupervised	An active (sham intervention) control condition was employed consisting of flexibility and relaxation activities.
Ochi et al. 2022 Japan	Breast 50 (100)	Intervention: 25 Control: 25	Intervention- 48 (6) Control- 49 (5)	50 (100) female	After treatment 12 weeks	HIIT, personalized, body weight exercises delivered via a smartphone app	High	10 min sessions, 3x/week	Home-based, unsupervised	Control group received a smartwatch for 12 weeks
Cuesta-Vargas et al. 2014 Spain	Breast 42 (100)	Intervention: 22 Control: 20	Intervention: 47.3 (6.6) Control: 48.7 (9.7)	42 (100) female	After treatment 8 weeks	Deep water running, land-based mobility and strengthening exercise	Moderate-high	60 min sessions 3x/week	setting not reported, supervised	Usual care

Kampshoff et al. 2018 The Netherlands	Overall n= 277 Breast 181 (65) Colon 49 (17) Lymphoma 26 (12) Ovarian 12 (4) Cervix 4 (1) Testis 5 (1)	High intensity: 139 Low to moderate intensity: 138	High intensity: 54 (10.7) Low to moderate intensity: 53 (11.4)	High intensity: 29 (21) male, 110 (79) female Low to moderate intensity: 26 (19) male, 112 (81) female	After treatment 12 weeks	Aerobic interval and muscular strength training	Low-moderate vs high	2x/week session duration NR	Clinic-based, supervised	Wait-list control (usual care)
May et al. 2017 The Netherlands	Breast 204 (86)	Full study: intervention- 102, control-102 Included in CUA: intervention- 87, control- 78	Intervention- 50.0 (7.9), control- 49.4 (7.6)*	165 (100) female*	During treatment 18 weeks	Aerobic interval and muscular strength training	Moderate	1 hour sessions 2x/week	Clinic-based, supervised	Usual care
	Colon 33 (14)	Full study: intevention-17, control-16 Included in CUA: intervention- 14, control- 15	Intervention- 57.4 (11.2), control 59.1 (8.9)*	Intervention- 7 (50) male, 7 (50) female, control- 11 (73) male, 4 (27) female*						
van Dongen et al. 2019 The Netherlands	Overall n= 109 Multiple myeloma 58 (53) non-Hodgkin lymphoma 51 (47)	Intervention: 54 Control: 55	Intervention: 52 (11) Control: 53 (12)	Intervention: 32 (59) male, 22 (41) female Control: 37 (67) male, 18 (33) female	After treatment 18 weeks	Aerobic interval and muscular strength training	High	60 min sessions, 2x/week for 1st 12 weeks, 1x/week for last 6 weeks	Clinic-based, supervised	Usual care
Edmunds at al. 2020 Australia	Prostate 100 (100)	Intervention: 50 Control: 50	Intervention: 71.9 (5.6) Control: 71.5 (7.2)	100 (100) male	After treatment 6 months	Aerobic and resistance training	Moderate-high	60 min sessions, 2x/week	Clinic-based, supervised	Control group: pedometer and a modified educational booklet with physical activity guidelines (150 min per week, moderate intensity)
Rosero et al. 2020 Spain	Non-small-cell lung 34 (100)	Intervention: 21 Control: 13	Intervention: 74.5 (3.6) Control: 79.0 (3.0)	Intervention: 15 (79) male, 4 (21) female Control: 5 (71) male, 2 (29) female	During treatment 10 weeks	Aerobic, resistance, balance/coordination, and flexibility training	Moderate	45-50 min sessions, 2x/week	Research clinic, supervised	Usual care

*Participants included in the economic evaluation only

**Timepoint is in relation to cancer treatment

CUA- cost-utility analysis

Utility Measures Results

Nine studies used the EQ-5D-3L (Cuesta-Vargas et al., 2014; Gordon et al., 2017; Haines et al., 2010; Kampshoff et al., 2018; May et al., 2017; Ochi et al., 2022; Rosero et al., 2020; van Dongen et al., 2019; van Waart et al., 2018) and one study used the SF-6D (Edmunds et al., 2020). Only five studies (50%) reported utility scores, including individuals with breast cancer (n=579) and colon cancer (n=29), and used the EQ-5D-3L to derive utilities (Cuesta-Vargas et al., 2014; Gordon et al., 2017; Haines et al., 2010; May et al., 2017; Ochi et al., 2022). Three of these studies also included CUAs (Gordon et al., 2017; Haines et al., 2010; May et al., 2017). Four studies found no statistically significant results ($p > 0.05$) for utility scores (Cuesta-Vargas et al., 2014; Haines et al., 2010; May et al., 2017; Ochi et al., 2022). Only one RCT found a clinically meaningful and significant change ($p=0.037$) in utility scores (+0.07) over time, favoring the intervention group (n=127), and a clinically meaningful difference between groups compared with usual care (n=60) during an 8-month program (Gordon et al., 2017). In this study, the authors considered a difference of ≥ 0.06 of the EQ-5D-3L to be clinically meaningful, which aligns with other research on the MCID of utilities (Gordon et al., 2017). Four of the remaining studies calculated utilities for the CUA but did not report the values, only the QALYs gained and ICERs. Three of these studies used the EQ-5D-3L (Kampshoff et al., 2018; van Dongen et al., 2019; van Waart et al., 2018) and one used the SF-5D (Edmunds et al., 2020). One study, which used the EQ-5D-3L, did not include a CUA nor calculate utilities. Instead, the authors calculated an overall score by summing the score for each domain (Rosero et al., 2020), which is not a validated method for scoring the EQ-5D-3L (EuroQol Research Foundation, 2018). Results of all studies are summarized in Table 2.3.

Table 2.3. Study characteristics and findings.

Study/country	Study design	Reason for including generic utility measure	Measure used/ timing of measurement	Main Findings			
				EQ-VAS scores	Utility scores	QALYs	ICERs
Breast Cancer Only							
Gordon et al. 2017 Australia	Cost-utility/cost-effectiveness analysis of an RCT	To calculate QALYs for the economic evaluation	EQ-5D-3L Baseline (6 weeks post-surgery), six months post-surgery, 12 months post-surgery	Not reported	Intervention: 0.79 (BL), 0.83 (6 months), 0.86 (12 months) Control: 0.83 (BL), 0.81 (6 months), 0.85 (12 months) Clinically important within group change in intervention group from baseline to 12 months p-value: 0.037*	Incremental gain in exercise group was 0.009 QALYs (95% CI not reported)	Model 1 (service provider model): AUD$105 231 and model 2 (private model): AUD$90 842
van Waart et al. 2018 The Netherlands	Cost-utility/cost-effectiveness analysis of an RCT	To calculate QALYs for the economic evaluation	EQ-5D-3L Baseline, every three months during chemo, end of chemo, 3- and 6-months post chemo	Not reported	Not reported	Incremental gain in exercise group was 0.04 QALYs (95% CI 0.01-0.08)	Exercise versus UC was €26,916/QALY
Haines et al. 2010 Australia	RCT with cost-utility/cost-effectiveness analysis	To evaluate both efficacy and economic efficiency	EQ-5D-3L Baseline, 3 months, 6 months	Intervention: 72.6 (BL), 80.6 (3 months), 80.4 (6 months) Control: 77.5 (BL), 74.1 (3 months), 79.3 (6 months) p-value: 0.09*	Intervention: 0.81 (BL), 0.78 (3 months), 0.80 (6 months) Control: 0.85 (BL), 0.84 (3 months), 0.83 (6 months) p-value: 0.87	QALYs were -0.01 (full dataset) and 0 (outliers excluded) (95% CI's not reported)	AUD$484,884/QALY (full dataset) or AUD$340,391/QALY (outliers excluded)
May et al. 2017 The Netherlands (Breast cancer subgroup)	Cost-utility/cost-effectiveness analysis of an RCT	To calculate utilities and QALYs for the economic evaluation	EQ-5D-3L Every four weeks for 36 weeks	Not reported	Intervention: 0.88 (BL), 0.82 (36 weeks) Control: 0.87 (BL), 0.82 (36 weeks)	Incremental gain in exercise group was 0.01 QALYs (95% CI −0.02-0.03)	€403 394/QALY
Ochi et al. 2022 Japan	RCT	To measure HRQL	EQ-5D-3L Baseline, 12 weeks	Not reported	Intervention: 0.95 (BL), 0.92 (12 weeks) Control: 0.94 (BL), 0.88 (12 weeks)p-value: 0.25	Not reported	Not reported

Cuesta-Vargas et al. 2014 Spain	Non-randomized controlled intervention study	To measure quality of life	EQ-5D-3L Baseline and 8 weeks	Intervention: 28.3 (BL) 49.6 (8 weeks) Control: 29.3 (BL), 32.5 (8 weeks) p-value: 0.001*	Intervention: 0.29 (BL), 0.32 (8 weeks) Control: 0.28 (BL), 0.33 (8 weeks) p-value: 0.068	Not reported	Not reported
Other Cancers							
Kampshoff et al. 2018 The Netherlands	RCT with cost-utility/cost-effectiveness analysis	To calculate QALYs for the economic evaluation	EQ-5D-3L Baseline, 12 weeks, 64 weeks	Not reported	Not reported	Incremental gain in exercise group was 0.028 QALYs (95% CI −0.006- 0.061)	Cost savings of €87,831 per QALY gained in high intensity exercise compared with low intensity exercise
May et al. 2017 The Netherlands (Colon subgroup)	Cost-utility/cost-effectiveness analysis of an RCT	To calculate utilities and QALYs for the economic evaluation	EQ-5D-3L Every four weeks for 36 weeks	Not reported	Intervention: 0.89 (BL), 0.89 (36 weeks) Control: 0.82 (BL), 0.79 (36 weeks)	Incremental effect was 0.03 QALYs	Cost-savings of €4321/QALY
van Dongen et al. 2019 The Netherlands	RCT with cost-utility/cost-effectiveness analysis	To calculate QALYs for the economic evaluation	EQ-5D-3L Baseline, post-intervention, 1 year after PI assessment	Not reported	Not reported	Incremental change in exercise group was -0.07 QALYs (95%CI -0.17-0.04)	-€8043, indicating that the intervention was more costly and less effective than usual care
Edmunds at al. 2020 Australia	Cost-utility/cost-effectiveness analysis of an RCT	To calculate QALYs for the economic evaluation	SF-6D Baseline, 6 months, 12 months	Not applicable	Not reported	Incremental gain in exercise group were 0.0085 QALYs (95% CI −0.0093-0.0256)	AUD$64,235/QALY
Rosero et al. 2020 Spain	Non-randomized controlled intervention study	To measure self-perceived physical function and health status/health-related quality of life	EQ-5D-3L Baseline and 10 weeks	Intervention: 69.05 (BL) 73.26 (10 weeks) Control: 72.29 (BL), 72.14 (10 weeks) p-value: 0.571	Not reported	Not reported	Not reported

Note: ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year, RCT: randomized controlled trial, BL: baseline, HRQL: health-related quality of life
* Indicates statistically significant result

All seven articles that included a CUA reported results for QALYs. Five of these studies found an incremental gain in QALYs with exercise compared to control (Edmunds et al., 2020; Gordon et al., 2017; Kampshoff et al., 2018; May et al., 2017; van Waart et al., 2018). The largest gain was 0.04 QALYs (95% CI 0.01–0.08) and was found in a study of individuals with breast cancer who exercised during chemotherapy (van Waart et al., 2018). The ICER for this study was EUR 26,916/QALY, which may be considered cost-effective depending on the willingness-to-pay threshold, which in the Netherlands is reported to range from EUR 20,000 to EUR 80,000 (Reckers-Droog et al., 2021). The smallest gain was 0.0085 QALYs (95% CI −0.0093–0.0256). This study included individuals with prostate cancer who exercised after treatment, and resulted in an ICER of AUD 64,235/QALY, which is unlikely to be cost-effective as it exceeds the typical Australian willingness-to-pay threshold of AUD 50,000 (Edmunds et al., 2020). One study found a decrease of 0.07 QALYs (95%CI −0.17–0.04) in individuals with hematological cancers who exercised after treatment (van Dongen et al., 2019). The ICER for this intervention was −8043, indicating that the intervention was more costly and less effective than usual care (van Dongen et al., 2019). Another study found a decrease of 0.01 QALYs (95% CI not reported) and no change when outliers were excluded (Haines et al., 2010). This study included individuals newly diagnosed with breast cancer and the intervention took place during treatment, and resulted in ICERs of AUD 484,884/QALY (full dataset), well above the threshold of AUD 50,000/QALY (Haines et al., 2010).

Discussion

Our review findings indicate that generic utility measures are not commonly included in exercise oncology studies. Furthermore, an evidence gap was seen in the reporting of generic utility measures in exercise oncology studies. While four studies calculated utilities for a CUA,

they did not report the actual utility scores, only the QALYs and ICERs (Edmunds et al., 2020; Kampshoff et al., 2018; van Dongen et al., 2019; van Waart et al., 2018). Although two of these studies had favourable ICERs (Kampshoff et al., 2018; van Waart et al., 2018), utility scores help to characterize the baseline health status of the study sample, and inform the magnitude and direction of change over time. Moreover, the values allow comparison across studies and can indicate whether the change was meaningful to participants. When considering the cost per QALY as the primary outcome for economic evaluations, we found contradictory and inconclusive results, which are similar to findings in systematic reviews of economic analyses in exercise oncology (Gubler-Gut et al., 2021; Khan et al., 2019; Wang et al., 2023). Similar to these reviews, we noted variability in patient characteristics, time horizons, and exercise parameters of the included studies, which probably contributed to the mixed results. Overall, these findings support the need for further research with larger sample sizes.

Our findings suggest that there is an evidence gap in our understanding of the optimal exercise type, timing, and intensity. For example, consistent with previous reports (Gubler-Gut et al., 2021), higher intensity interventions show promise for being cost-effective when delivered posttreatment. This finding was supported by the study by Kampshoff and colleagues involving 277 individuals with mixed cancer types, where the exercise intervention took place following completion of chemotherapy (Kampshoff et al., 2018). The authors found that high intensity aerobic and strength training showed benefits for outcomes of fatigue and anxiety, and was cost-effective compared with low-moderate-intensity exercise (Kampshoff et al., 2018). On the other hand, a study conducted by van Dongen and colleagues examined high-intensity exercise for individuals with multiple myeloma and non-Hodgkin lymphoma who were undergoing treatment involving autologous stem cell transplantation (van Dongen et al., 2019). The authors reported

that high-intensity exercise did not result in significant changes in fitness nor fatigue, and was also not cost-effective when compared with usual care (van Dongen et al., 2019). While the discordant findings may be explained by differences in the timing of the intervention in relation to cancer treatment (following versus during intensive treatment), the results were probably also influenced by patient characteristics (e.g., stage of cancer) and differences in completion rates between the two studies (i.e., 75% and 54%, respectively).

The setting and supervision of exercise programs may also be an important factor in determining both effectiveness and cost-effectiveness. While both supervised and unsupervised exercise have advantages and disadvantages, the optimal approach for people with cancer remains a source of debate (Adams et al., 2018; Hardcastle & Cohen, 2017, 2018; Kraemer et al., 2022; Lopez et al., 2018; Newton et al., 2018; Pelosi et al., 2023). In this review, only two unsupervised, home-based interventions were included, and conclusions cannot be made regarding the effects setting and supervision have on utility scores, QALYs, and cost-effectiveness.

Economic evaluations, given their focus on costs and treatment effects, require careful consideration of research methodology pertaining to study power and the time horizon for collection of outcome effects (Yousefi et al., 2016). For example, two breast cancer-specific studies, both of which took place in the Netherlands during treatment and were similar in duration, frequency, and type of exercise, resulted in vastly different ICERs of EUR 26,916/QALY (van Waart et al., 2018) and EUR 403 394/QALY (May et al., 2017). This large difference in ICERs may be explained partially by the differences in the reported healthcare and societal costs between the two studies. May and colleagues reported higher costs, length of hospital stay, and sick leave compared with control participants (May et al., 2017), whereas van

Waart and colleagues reported a more favourable ICER, while healthcare and societal costs did not differ significantly across groups (van Waart et al., 2018). Better chemotherapy completion rates in the supervised exercise group (a finding consistent with the study by May and colleagues) led to higher chemotherapy costs. While costs were higher with exercise, better chemotherapy completion is associated with improved cancer survival outcomes (An et al., 2021; Mijwel et al., 2020; van Waart et al., 2015), suggesting the need for longer-term follow-up of cancer outcomes, and the potential for underestimation of the cost-effectiveness of exercise. A recent systematic review by Wang and colleagues found that five of six (83%) studies that used decision-analytic modelling to extrapolate long-term health effects of exercise (3 years to lifetime) were cost-effective, whereas only five of ten (50%) trial-based analyses were cost-effective. Time horizons for the trial-based analyses ranged from 9 to 16 months (Wang et al., 2023).

Another important finding was related to limitations inherent in the chosen health utility measures, namely, the reported ceiling effects and poor sensitivity to change associated with the EQ-5D-3L, a health utility measure that was used in nine of the ten studies in this review. The EQ-5D-5L has been shown to have increased sensitivity and precision over the 3L version, and is recommended for future work (Janssen et al., 2018). Moreover, unlike condition specific measures, generic utility measures often do not assess the central domains of HRQL for a specific disease such as cancer. For example, the EQ-5D does not have a measure of energy or fatigue, which is a commonly reported symptom that is important to adults with cancer (Teckle et al., 2011). The generic utility measures may not be as responsive to change as a condition-specific measure; however, they can complement their use by providing a multidimensional construct that allows comparison of cost-effectiveness across interventions and disease

conditions. Thus, generic utility measures are important to facilitate economic evaluations of exercise oncology programs, but are most informative when findings are considered in addition to, not instead of, cancer specific HRQL measures.

Studies in our review largely involved individuals with breast cancer. This finding is not surprising, given that a majority of research in the exercise oncology field has focused on women with breast cancer (Cormie et al., 2017). However, this population gap limits the generalizability of our results to other cancer types. Moreover, most of the studies included in this review were supervised, in-person interventions. Only one study was found that used a health application to deliver the exercise intervention. Future studies involving the use of technology should consider inclusion of generic utility measures to inform cost-effectiveness. Given the heterogeneity in patient characteristics, timing of exercise interventions and exercise programming features, more large-scale studies are warranted, especially in cancers other than breast cancer.

Conclusions

Generic utility measures are important to inform economic evaluations; however, to date, they have been underutilized in exercise oncology studies. We identified research gaps relative to evidence, methodology, and population (Figure 2.2). To provide more rigorous economic evaluations of exercise in oncology, researchers should report utility scores when conducting CUAs, in addition to QALYs and ICERs. Findings related to utility scores should be considered alongside other key metrics including the impact of exercise on cancer-related symptoms, fitness, and quality-of-life outcomes. Despite the limited evidence of cost effectiveness, the established evidence supporting the benefit of exercise for health-related quality of life, physical functioning, fatigue, anxiety, and depression supports consideration for inclusion in standard care (Campbell et al., 2019; Cormie et al., 2017; Stout et al., 2017).

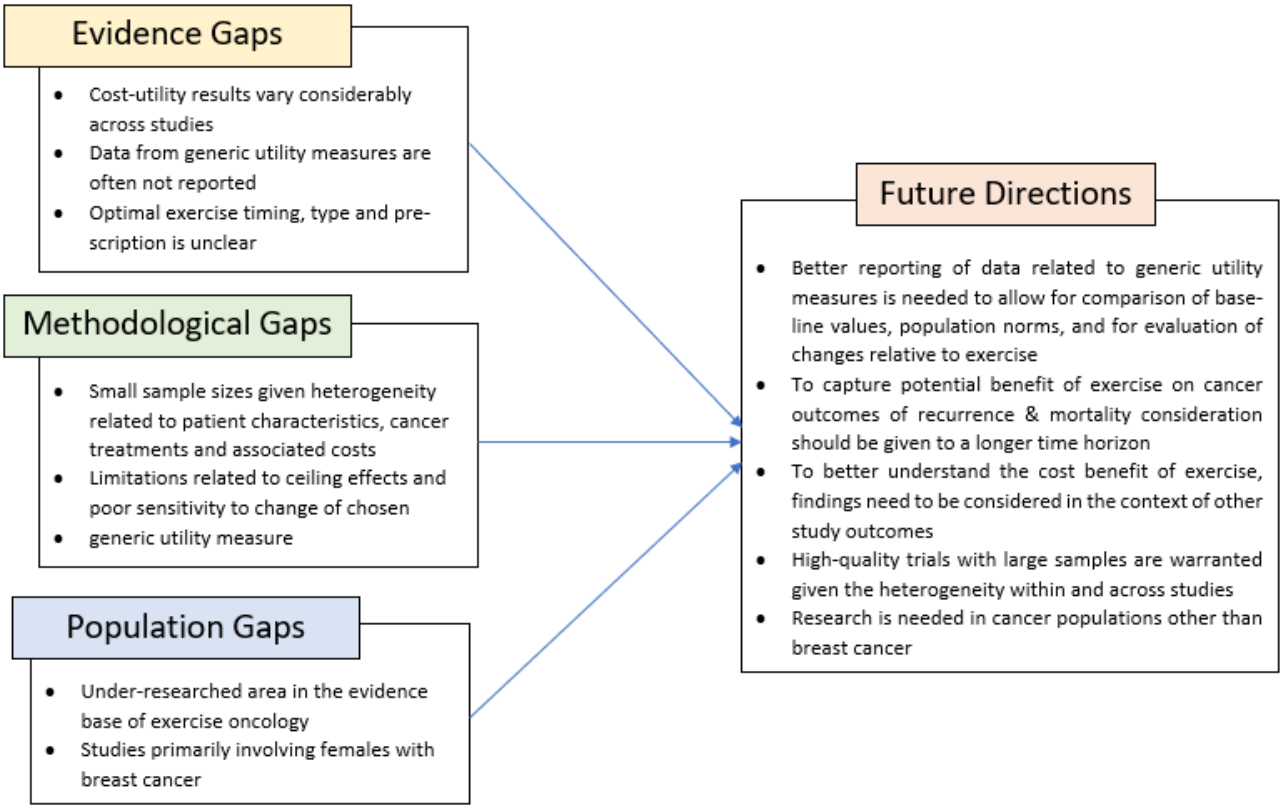

Figure 2.2: Identified research gaps and future considerations in exercise oncology research

CHAPTER 3: SYMPTOM BURDEN IN ADULTS WITH HEMATOLOGICAL CANCER PARTICIPATING IN COMMUNITY-BASED EXERCISE

Introduction

The number of people diagnosed with cancer each year in Canada has been steadily rising, primarily due to Canada's aging and growing population (Brenner et al., 2022). In recent decades, advances in both cancer treatments and early detection have led to substantial increases in survival rates for many cancers. The largest increases in 5-year net survival for all cancers since the early 1990s have been for hematological cancers (Canadian Cancer Society Advisory Committee, 2023).

Consequently, there is a growing population of individuals with hematological cancer, many of whom experience physical and psychological symptoms caused by the disease. Symptom burden is a summative indicator of the severity and impact of multiple symptoms experienced by an individual and is an important measure of the impact of cancer and its treatment on individuals (Cleeland, 2007). With the increases in survival of many hematological cancers, there is a need for more research examining how best to manage both cancer-related, and treatment-related symptoms in this population. While there is evidence demonstrating benefit from exercise for individual symptoms (Abo et al., 2021; Knips et al., 2019; Xu et al., 2022), little is known about the effects of exercise on symptom burden in individuals with hematological cancer. Furthermore, little is known about the variables (socio-demographic, behavioural, and medical) that are associated with symptom burden in individuals with hematological cancers in the context of a community-based cancer-specific exercise program.

Methods

Study design

This study is a secondary analysis of data from the Alberta Cancer Exercise Hybrid Effectiveness-Implementation study (ACE) (McNeely et al., 2019). The objectives of this secondary analysis are 1) to examine the effectiveness of a cancer-specific 12-week exercise program on self-reported total and physical symptom burden as measured by ESAS-r in adults with hematological cancers and 2) to identify the baseline socio-demographic, behavioural, and medical variables associated with 12-week ESAS-r total symptom score and change in total symptom burden score from baseline to 12 weeks.

The ACE study is a single group hybrid effectiveness implementation study examining the benefit and implementation of a province-wide 12-week community-based cancer-specific exercise program (McNeely et al., 2019). Programming began in Edmonton and Calgary in January 2017, with programming rolled out to smaller urban centers in Alberta including Red Deer, Lethbridge, Medicine Hat, Grande Prairie, and Fort McMurray over the course of the study. The study sample size comprised 2,570 individuals who were on active cancer treatment or had completed treatment within a 3-year period. Recruitment was completed in February 2023. The five smaller cities were chosen because they are the largest cities in the province outside of the Edmonton and Calgary metropolitan areas. All seven cities have a tertiary, regional or community cancer centre. Programing is delivered through two hub sites with northern and central Alberta (Edmonton, Red Deer, Grande Prairie, Fort McMurray) managed by a study team at the University of Alberta and southern Alberta (Calgary, Lethbridge, Medicine Hat) managed by a team at the University of Calgary, with all sites adhering to the same protocol.

Participants

Inclusion criteria for this analysis included:

1) 18 years of age or older
2) Diagnosis of any type of hematological cancer
3) Either pre-treatment or receiving active cancer treatment or within three years of completing cancer treatment or have existing long-term or late presenting effects of their cancer treatment (e.g. cancer-related lymphedema)
4) Able to provide informed written consent in English

Study brochures were provided to the outpatient clinics at the cancer centres in all cities where programming took place. In Calgary, formal promotion included social media, videos in clinic waiting rooms, posters placed at the Tom Baker Cancer Centre and Holy Cross Centre, and prescription pads were provided to the oncology teams. Oncologists and other members of the care team such as physical therapists could recommend the study to individuals; however, individuals were also able to self-refer to the program. Individuals with metastatic disease, and those diagnosed with brain, lung, pancreatic, multiple myeloma, or head and neck cancer were required to have oncologist approval prior to enrolling in the study.

Intervention

Three 12-week sessions occurred each year over the duration of the study, starting in January (winter), April (spring), and September (fall). Participants joined at the beginning of a session and exercised with the same group of individuals for the 12 weeks. Exercise sessions included a combination of cardiovascular, strength, balance, and flexibility training. Intensity was set at 3-4 metabolic equivalent (MET) units per session at the start of the intervention and

progressed to 4-5 MET units over the 12 weeks (McNeely et al., 2019). Supervised exercise sessions occurred twice a week and were one hour in length.

Instructors were community-based qualified exercise professionals (QEPs: certified personal trainers, kinesiologists, and certified group fitness instructors) or Clinical Exercise Physiologists (CEPs) who worked in the centres where programming took place. All instructors were required to take the *ACE Cancer and Exercise Training for Fitness Professionals* online course offered through the University of Calgary. This 16-hour course includes content related to cancer biology, cancer incidence, treatment and treatment-related effects, exercise evidence and prescription for individuals with cancer, and health behaviour change. Hub-based cancer-specific CEPs were available to offer additional support to community-based QEPs and CEPs when necessary.

Exercise sessions were either circuit-based group classes or group personal training. Only two sites, both located in Edmonton, offered group personal training. At these sites participants performed their exercises individually under the supervision of an exercise professional at a ratio of one exercise professional to 5-8 participants. Circuit classes were conducted in small groups of 8-15 participants and with class size dependent on demand for each site. There were six sites in Edmonton and seven in Calgary. In the five smaller cities, only one site with a single class option was available per session.

Due to the COVID-19 pandemic, in the spring of 2020, programming transitioned to virtual circuit-based exercise classes that were delivered via an online video conference platform. From Fall 2020 to April 2023, both virtual and in-person options were offered although in-person options were not always available at every site. To participate in the virtual classes, participants had to have an internet connection and a device with a camera to connect to the class

(computer, tablet, or phone), and could reside anywhere in Alberta. Differences between the three modes of program delivery are detailed in Table 3.1.

Because the aim of the ACE study was to implement community-based exercise into standard care, the study was designed to be pragmatic, where there was some flexibility in the exercise prescription based on the equipment available and preference of the instructor; however, all instructors followed the same exercise protocol and principles. Exercise specialists were given a protocol template to follow which indicated the components to include (cardio, upper and lower body strength, balance, and flexibility) and which muscle groups to target; however, the individual instructor could select the specific exercises. For example, an upper body pulling and pushing exercise was required in each session; however, the exercise specialist could modify the movement or exercise (e.g., overhead press, lateral raise etc.). Moreover, QEPs and CEPs modified and tailored exercises for individual participants when necessary.

Table 3.1: ACE exercise intervention modes of delivery

Program Type	**In- person class**	**In-person group personal training**	**Virtual class**
Type of exercise equipment	Varied depending on what was available at each site. Typically included free weight, steps, mats	Cardio machines, weight machines, free weights, cable machines, mats	Exercise bands, free weights/alternatives
Exercises	Resistance exercises targeting all major muscles groups, balance, aerobic activities, and stretching	Aerobic activities, a series of resistance exercises targeting all major muscles groups, a balance exercise, and stretching	Resistance exercises targeting all major muscles groups, balance, aerobic activities, and stretching
Setting	YMCAs, municipal fitness centres, University of Calgary Thrive Centre	Wellspring Edmonton, University of Alberta Cancer Rehabilitation Clinic	Virtual

To ensure fidelity to the protocol, ACE staff conducted site visits. In Edmonton, when a new exercise specialist started, ACE staff would attend the first 48 in-person classes. In Calgary and the smaller cities, ACE staff attended first and last classes of each session. For virtual classes, ACE staff moderated each class and assisted the instructor through the program. At all locations ACE staff conducted the baseline, post-intervention, and follow-up assessments. Adherence was reported as percent of sessions attended. Attendance was tracked by instructors and the reason for missed sessions was reported if known. Adverse events were recorded by the instructor and reported to the ACE Lead/ ACE project coordinator.

Assessments

Participants completed fitness assessments and patient-reported outcome measures at baseline, and post-intervention (12 weeks). Depending on the site, further fitness testing was conducted at 24 weeks, and 1 year.

Outcome measures

The Edmonton Symptom Assessment System (ESAS) is a patient-reported measure of symptom burden originally developed for individuals with advanced cancers (Bruera et al., 1991). A revised version of the original ESAS that is commonly used today is known as the ESAS-r (Watanabe et al., 2011). This version includes nine symptoms: pain, tiredness, drowsiness, nausea, lack of appetite, shortness of breath, depression, anxiety, and overall well-being. Each symptom is measured by a single item numeric rating scale from zero (no symptom/best possible well-being) to 10 (worst possible symptom/worst possible well-being) based on how they feel at the time of completion (Watanabe et al., 2011). A copy of the ESAS-r can be found in Appendix A.

Scores for each symptom can be examined individually and summary scores can be calculated (Hui & Bruera, 2017). Three summary scores have been validated: physical, emotional, and total symptom distress. The physical score is the sum of the scores for pain, tiredness, nausea, drowsiness, lack of appetite, and shortness of breath (score range 0-60). The emotional score is the sum of scores for anxiety and depression (range 0-20). The total symptom distress score is the sum of all nine symptoms scores (range 0-90) (Hui & Bruera, 2017). Higher scores represent higher symptom burden. The ESAS-r is routinely used in oncology, palliative care, and nephrology both in clinical practice and research (Hui & Bruera, 2017). Common clinical applications include symptom screening and longitudinal symptom monitoring. The ESAR-r has been used to investigate symptom trajectory, symptom clusters, symptom modulators, and effectiveness of interventions in a variety of cancers (Hui & Bruera, 2017).

A review of psychometric studies concluded that the ESAS has good reliability, with test-retest reliability generally exceeding 0.8 (Richardson & Jones, 2009). Validity of the ESAS-r has not been well studied, with most validity studies using earlier versions of the ESAS. However, the limited literature that exists suggests that the ESAS-r is valid for use in individuals with cancer (Noel et al., 2021; Watanabe et al., 2012). Anchor based minimally clinically important differences (MCIDs) of ≥3 for total symptom burden and ≥3 for physical symptom burden have previously been identified (Hui et al., 2016). The ESAS-r is administered at each clinic visit for individuals with cancer across all Cancer Care Alberta sites in the province.

The primary outcome for this analysis is ESAS-r total symptom burden and secondary outcomes are ESAS-r physical symptom burden, ESAS-r tiredness, and ESAS-r drowsiness.

Independent Variables

Health is affected directly and indirectly by many factors including the social and physical environments, genetics, individuals' behaviour and biology, and disease-related factors (Evans & Stoddart, 1990). Symptom status is considered a component of health status that is directly affected by individual characteristics, biological and physiological variables, and psychological supports (Wilson & Cleary, 1995). Building on these frameworks, we suggest that symptom status is directly related not only to psychological supports and biological variables as Wilson and Clearly suggest in their model but also to social and economic variables. The Evans & Stoddart framework suggest health and function are directly related to individual behaviour, which is influenced by the social and physical environments. Building on this, we suggest that individual behaviour also relates directly to symptom status, which is a component of health and function (Figure 3.1). This adapted framework, along with the relevant literature on both symptom burden and exercise for adults with hematological cancers, guided this analysis. Social-demographic variables that have previously been shown to be associated with symptom burden in a cancer population include income (Bubis et al., 2018; Shi et al., 2011), employment status (Shi et al., 2011), education (Shi et al., 2011), and health insurance (in the United States where there is no universal healthcare) (Shi et al., 2011). We also included program type (i.e. in-person or virtual) and adherence as these are important variables in exercise research.

Socio-demographic variables

Socio-demographic variables including annual household income, marital status, education, employment status, gender, and ethnicity were self-reported at baseline. Sex assigned at birth was self-reported and age was calculated on the day of baseline fitness assessment using participant's date of birth.

Behavioural variables

Behavioural variables, including physical activity level, smoking status, and drinking status were self-reported at baseline. Physical activity level was measured using the Godin-Shepherd Leisure-Time Physical Activity Questionnaire (Appendix B) (Amireault et al., 2015b, 2015a; Amireault & Godin, 2015).

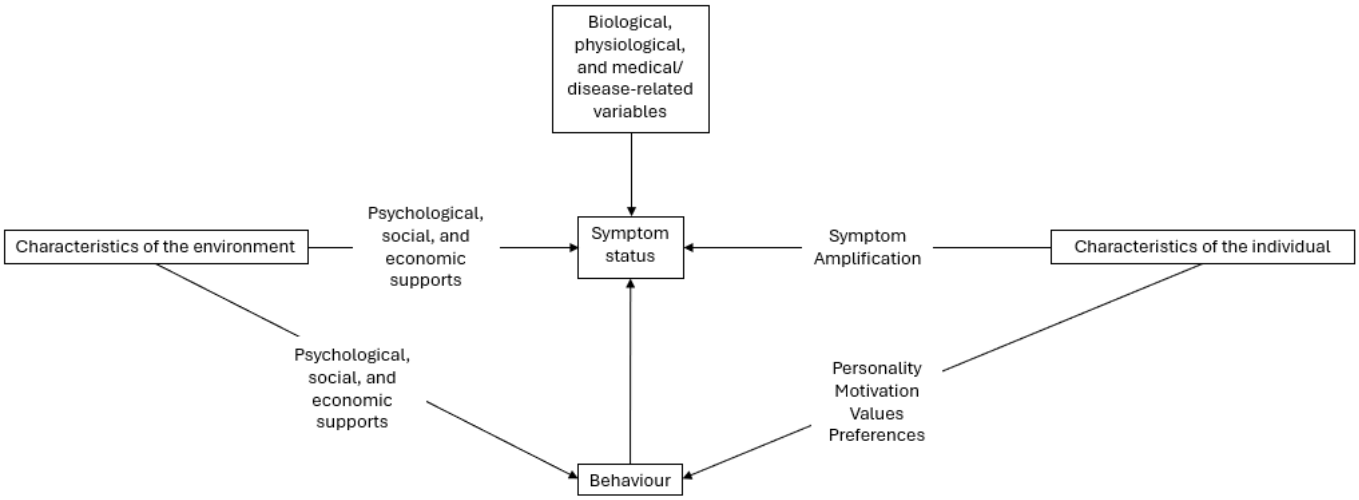

Figure 3.1: Conceptual Framework: adapted from Evans & Stoddart and Wilson & Cleary

Medical variables

Current and completed treatments were self-reported. Current treatment status was dichotomized into on systemic therapy (chemotherapy or targeted therapy) and not on systemic therapy. Cancer type, stage, and date of diagnosis were abstracted from cancer registry data (Appendix C). Time since diagnosis was calculated using participant's date of diagnosis and date of baseline fitness test. The number of co-morbidities were determined based on participant's self-reported answers on the Physical Activity Readiness Questionnaire (PAR-Q+) which is a standard form used to determine if exercise is safe and appropriate for a potential study participant (Appendix D). The PAR Q+ is completed during the screening process prior to beginning the study. BMI was calculated from height and weight measured by a research

assistant except for when fitness assessments were done virtually (i.e. during COVID), in which case height and weight were self-reported by participants.

Data analysis

Data were cleaned prior to analysis and all variables were examined for missing responses. Statistical analyses were performed using SPSS version 29. All statistical testing was performed with two-tailed tests ($p < 0.05$). All continuous variables were examined for normal distributions by comparing the mean, standard deviation, median, inter-quartile range, skewness, and examining histograms. For categorical variables, frequencies and percentages were examined. Continuous variables that were not normally distributed were categorized. For categorical variables, if less than 5 participants are in a single category it was collapsed into another category.

Objective 1

To examine the effectiveness of the cancer-specific 12-week exercise intervention on self-reported symptom burden paired, t-tests were used to compare the difference between the ESAS-r total score and physical scores before and after the exercise intervention. As fatigue is the most common symptom reported by participants in ACE, t-tests were also used to evaluate the effectiveness of exercise on tiredness and drowsiness. To evaluate change over time, the effect size was calculated by dividing the mean change score by the baseline standard deviation (Deyo & Patrick, 1995).

Objective 2

Change in ESAS-r score was dichotomized to improver and non-improver. For the purpose of this study, an improver was defined as someone who experienced an improvement equal to or greater than the MCIDs of 3 for total score and 3 for physical score (Hui et al., 2016).

Furthermore, due to the ESAS-r's floor effect, participants with a baseline score of 1, 2, or 3 were classified as improvers if they improved by at least 1 point and participants with a baseline score of 0 were classified as improvers if their symptom score remained at 0 at 12-weeks.

Multiple linear regression was used to identify the baseline socio-demographic, behavioural, and medical variables associated with 12-week ESAS-r total scores. Variables found to be statistically significant at $p < 0.2$ in the univariable analysis were included in the first multivariable model. Independent t-tests and ANOVAs were used to test categorical variables while Pearson's correlation was used to test continuous variables. For the final model, variables with the highest p-values were eliminated sequentially, using backward elimination method. The final models included statistically significant variables ($p < 0.05$), as well as age, sex, baseline ESAS-r score, and adherence.

The final regression model was assessed for multicollinearity by examining correlation matrixes and variance inflation factor (VIF) scores. A correlation >0.8 or a VIF score >2.5 (Johnston et al., 2018) is considered evidence of a possible multicollinearity issue. We compared the effect of removing each variable on the R^2 values and model coefficients to determine if either variable should be removed, while also considering if these effects were congruent with our theoretical frameworks. After performing the final regression models, the standard error of each independent variable was inspected for precision. The residual scatterplot was also examined to determine if the residuals were normally distributed.

Results

Participants

In total, 354 participants with hematological cancer were enrolled in ACE between January 2017 and January 2023. The baseline characteristics of all participants are shown in

Table 3.2. Participants were 49% (n=174) female and had a mean age of 59 years (SD 14.8). The majority of participants were married (73%, n=257) and had at least a college level education (66%, n=233). At baseline, only 16% (n=55) of participants reported meeting physical activity guidelines of at least 150 minutes of moderate to vigorous physical activity per week, while 56% (n=197) reported being completely sedentary (zero minutes of moderate or higher intensity exercise per week). While both sex and gender were collected at baseline, all participants in this analysis expressed gender identities that aligned with their assigned sex at birth (i.e. cis gender). Therefore, these two variables were fully correlated so we only included sex assigned at birth in our regression analysis. All participant characteristics can be found in Table 3.2.

Table 3.2: Participant Characteristics

	Total sample (n= 354)	**Improved in ESAS-r Total Symptom Burden (n=136)**	**Did not improve in ESAS-r Total Symptom Burden (n=190)**
Socio-demographic variables			
Age (years), mean (SD)	58.9 (14.8)	59.5 (15.3)	59.0 (14.3)
Sex, n (%)			
Female	174 (49.2)	62 (45.6)	97 (51.1)
Male	180 (51.8)	74 (54.4)	93 (48.9)
Marital status, n (%)			
Never married	41 (11.6)	19 (14.0)	18 (9.5)
Married/Common-law	257 72.6)	99 (72.8)	137 (72.1)
Separated/divorced/widowed	56 (15.8)	18 (13.2)	35 (18.4)
Ethnicity, n (%)			
White	270 (76.3)	100 (73.5)	155 (81.6)
Non-white	84 (23.7)	36 (26.5)	35 (18.4)
Education, n (%)			
Did not complete college/university	121 (34.2)	39 (28.7)	67 (35.3)
Completed college/university	233 (65.8)	97 (71.3)	123 (64.7)
Employment status, n (%)			
Disability	104 (29.4)	37 (27.2)	56 (29.5)
Retired	138 (39.0)	48 (35.3)	81 (42.6)
Employed full- or part-time	69 (19.5)	34 (25.0)	30 (15.8)
Homemaker/temporarily unemployed	43 (12.1)	17 (12.5)	23 (12.1)
Annual Household Income, n (%)			
<$60 000	117 (33.1)	45 (37.8)	61 (35.3)
$60 000+	200 (56.5)	74 (62.2)	112 (64.7)
Residential locale, n (%)			
Urban	311 (87.9)	121 (89.0)	166 (87.4)

Rural	43 (12.1)	15 (11.0)	24 (12.6)
Behavioural variables			
Physical Activity, n (%)			
Sedentary	197 (55.6)	81 (59.6)	99 (52.1)
Insufficiently Active	102 (28.8)	41 (30.1)	54 (28.4)
Sufficiently Active	55 (15.5)	14 (10.3)	37 (19.5)
Drinking Status, n (%)			
Never drank	38 (10.7)	15 (11.0)	18 (9.5)
Ex-drinker	36 (10.2)	12 (8.8)	17 (8.9)
Occasional/social drinker	269 (76.0)	103 (75.7)	151 (79.5)
Regular drinker	11 (3.1)	6 (4.4)	4 (2.1)
Smoking Status, n (%)			
Never smoked	215 (60.7)	87 (64.0)	113 (59.5)
Ex-smoker	124 (35.0)	42 (30.9)	71 (37.4)
Occasional/Regular smoker	15 (4.2)	7 (5.1)	6 (3.2)
Program type, n (%)			
Virtual	84 (23.7)	27 (19.9)	48 (25.3)
In-person	270 (76.3)	109 (80.1)	142 (74.7)
Medical variables			
Body Mass Index (kg/m^2), mean (SD)	27.5 (5.8)	27.8 (5.5)	27.1 (6.0)
Number of comorbidities, n (%)			
0-1	221 (62.4)	86 (63.2)	116 (61.1)
2+	133 (37.6)	50 (36.8)	74 (38.9)
Hematological cancer type, n (%)			
Hodgkin lymphoma	32 (9.0)	13 (9.6)	15 (7.9)
Non-Hodgkin lymphoma	123 (34.7)	56 (41.2)	60 (31.6)
Leukemia/other	116 (32.8)	42 (30.9)	60 (31.6)
Multiple myeloma	83 (23.4)	25 (18.4)	55 (28.9)
Cancer stage, n (%)			
Early stage/unknown	140 (39.5)	54 (39.7)	72 (37.9)
Advanced stage	214 (60.5)	82 (60.3)	118 (62.1)
Time since diagnosis			
<1 year	135 (38.1)	52 (38.2)	72 (37.9)
1-3 years	135 (38.1)	50 (36.8)	74 (38.9)
>3 years	84 (23.7)	34 (25.0)	44 (23.2)
Current treatment			
No systemic therapy	194 (54.8)	76 (55.9)	99 (52.1)
Systemic therapy	160 (45.2)	60 (44.1)	91 (47.9)
Completed treatments, n (%)			
Chemotherapy	285 (80.5)	106 (77.9)	157 (82.6)
Radiation therapy	108 (30.5)	39 (28.7)	61 (32.1)
Targeted therapy	18 (5.1)	7 (5.1)	9 (4.7)
Stem cell transplant	89 (25.1)	29 (21.3)	55 (28.9)
Surgery	42 (11.9)	12 (8.8)	28 (14.7)
Program variables			
Program type, n (%)			
Virtual	84 (23.7)	27 (19.9)	48 (25.3)
In-person	270 (76.3)	109 (80.1)	142 (74.7)
Adherence (%), mean (SD)	76.0 (25.0)	81.9 (18.9)	77.9 (21.9)

Of the 354 participants, 326 (92.1%) completed the 12-week ESAS-r questionnaire. Participants who did not complete the 12-week ESAS-r did not significantly differ from those who completed their 12-week ESAS-r in age, BMI, sex, marital status, income, education, employment status, drinking status, smoking status, baseline physical activity levels, treatment status, past treatments received, time since diagnosis, or cancer stage ($p > 0.05$). Non-white participants ($p < 0.001$), virtual participants ($p = 0.044$), and those with leukemia ($p = 0.006$) were more likely to have missing 12-week ESAS-r questionnaires. Mean adherence to the exercise intervention was 76.0% (SD 25.0%).

Effectiveness

Using paired t-tests, statistically significant improvement ($p < 0.05$) was observed for physical symptom burden, tiredness, and drowsiness but not for total symptom burden. Effect sizes were small for all variables (Table 3.3).

Table 3.3: Effectiveness Results

	Baseline Score Mean (SD)	**12-week Score** Mean (SD)	**Mean Difference** (95% CI)	**p-value**	**Effect size (SD)**
Total Symptom Burden	16.69 (11.75)	16.07 (12.14)	-0.62 (-1.68, 0.45)	0.255	0.051 (0.81)
Physical Symptom Burden	10.47 (7.99)	9.52 (8.18)	-0.94 (-1.72,-0.17)	**0.017**	0.114 (0.86)
Tiredness	3.48 (2.44)	3.12 (2.38)	-0.35 (-0.60, -0.10)	**0.006**	0.143 (0.92)
Drowsiness	2.28 (2.30)	2.00 (2.22)	-0.28 (-0.52, -0.04)	**0.021**	0.119 (0.92)

Statistically significant (<0.05)

Total Symptom Burden

One hundred thirty-six (38.4%) participants improved in total symptom burden by greater than or equal to the MCID of 3. We observed a higher percentage of participants improved in the non-Hodgkin lymphoma group, as well as participants who were sedentary or insufficiently

active at baseline, participants who were off treatment during the intervention and males. Furthermore, a lower percentage of improvers were observed in participants who were retired and those with a diagnosis of multiple myeloma.

Baseline differences in total ESAS-r score were observed for income, employment status, baseline physical activity and cancer type. Participants with lower income (<$60 000) had significantly worse baseline scores than those with higher income (p =0.005). Participants on disability had worse scores than those who were retired (p <0.001) and when compared to those who were employed full- or part-time (p =0.029). Participants who were sedentary at baseline had worse scores than those who were sufficiently active (p =0.034). As well, participants with Hodgkin lymphoma (p =0.006) and leukemia (p =0.019) had worse scores than those with multiple myeloma. At 12 weeks, the significant differences for income and employment status remained. Additionally, at 12 weeks, non-white participants had worse scores than white participants (p =0.048) and those with two or more co-morbidities had worse scores than those with one or no co-morbidities (p =0.016). Baseline and 12-week scores for all categorical variables are reported in table 3.4.

Table 3.4 Descriptives and univariable results for total symptom burden

	Baseline score, mean (SD)	**Univariable Analysis**	**12-week score, mean (SD)**	**Univariable Analysis**
Socio-demographic variables				
Age (years)		**0.004**		0.060
Sex				
Male	17.36 (12.02)	0.715	16.22 (11.82)	0.825
Female	16.89 (12.22)		15.92 (12.49)	
Annual Household Income				
<$60 000	19.45 (12.63)	**0.005**	18.32 (12.46)	**0.022**
$60 000+	15.52 (11.64)		14.91 (11.98)	
Marital status				
Married/Common-law	17.03 (12.05)	0.910	15.82 (12.26)	0.454
Never married	17.90 (13.28)		15.03 (12.08)	
Separated/divorced/widowed	17.02 (11.63)		17.91 (11.68)	

Education				
Completed college/university	16.67 (12.07)	0.317	16.11 (12.22)	0.934
Did not complete college/university	18.02 (12.16)		15.99 (12.03)	
Employment status				
Retired	14.29 (9.88)	**<0.001**	14.30 (9.88)	**0.003**
Disability	20.98 (13.61)		19.87 (13.71)	
Part-time	14.11 (11.17)		12.71 (10.21)	
Homemaker/temporarily unemployed	19.09 (13.18)		16.18 (13.05)	
Full-time	16.86 (11.70)		14.85 (13.31)	
Ethnicity				
white	16.47 (11.44)	0.096	15.38 (11.08)	**0.048**
Non-white	19.26 (13.87)		18.61 (15.24)	
Location				
Urban	17.25 (12.41)	0.605	16.16 (12.17)	0.731
Rural	16.23 (9.65)		15.45 (12.08)	
Behavioural Variables				
Physical Activity level				
Sedentary	18.41 (11.76)	**0.033**	16.72 (11.92)	0.383
Insufficiently active	16.49 (12.96)		15.94 (12.91)	
Sufficiently active	13.75 (11.08)		14.08 (11.42)	
Drinking Status				
Occasional/social drinker	17.43 (11.97)	0.088	16.37 (12.22)	0.067
Never drank	16.18 (11.75)		14.62 (10.65)	
Ex-drinker	18.50 (14.04)		18.20 (13.67)	
Regular drinker	8.45 (5.77)		7.00 (4.99)	
Smoking Status				
Never smoked	17.16 (11.48)	0.367	15.95 (11.51)	0.973
Ex-smoker	16.58 (12.58)		16.27 (13.01)	
Occasional/Regular smoker	21.27 (16.27)		16.23 (14.60)	
Medical variables				
BMI ($kg/m^{2)}$		0.052		0.207
Number of comorbidities				
0-1	16.67 (12.83)	0.357	14.82 (11.58)	**0.016**
2+	17.89 (10.79)		18.14 (12.79)	
Cancer type				
Non-Hodgkin lymphoma	17.51 (11.63)	**0.003**	15.44 (11.99)	0.052
Hodgkin lymphoma	21.44 (15.14)		20.76 (12.59)	
Leukemia/other	18.33 (13.06)		17.10 (13.36)	
Multiple myeloma	13.23 (8.87)		14.00 (10.07)	
Time since diagnosis				
<1 year	17.35 (11.30)	0.948	15.59 (11.14)	0.765
1-3 years	16.87 (12.16)		16.69 (13.22)	
>3 years	17.19 (13.34)		15.86 (11.97)	
Cancer stage				
Early stage/unknown	17.60 (13.22)	0.555	16.35 (12.68)	0.742
Advanced stage	16.82 (11.33)		15.90 (11.83)	
Current treatment				

Not on systemic therapy	16.84 (11.43)	0.614	15.35 (11.62)	0.244
On systemic therapy	17.49 (12.89)		16.92 (12.71)	
Completed chemotherapy				
No	16.06 (11.34)	0.413	15.83 (12.79)	0.859
Yes	17.39 (12.28)		16.13 (12.01)	
Completed radiation therapy				
No	17.24 (12.46)	0.782	15.56 (12.15)	0.246
Yes	16.87 (11.31)		17.25 (12.10)	
Completed targeted therapy				
No	17.10 (12.21)	0.847	16.15 (12.14)	0.611
Yes	17.67 (10.18)		14.56 (12.36)	
Completed stem cell transplant				
No	17.48 (12.18)	0.349	15.95 (12.09)	0.770
Yes	16.09 (11.86)		16.40 (12.36)	
Completed surgery				
No	17.41 (12.48)	0.117	16.14 (12.34)	0.773
Yes	15.02 (8.62)		15.55 (10.72)	
Program variables				
Program type				
Virtual	17.49 (12.27)	0.757	17.92 (12.75)	0.140
In-person	17.02 (12.07)		15.54 (11.93)	
Adherence (%)		**<0.001**		**<0.001**

Statistically significant (p <0.05)

Linear Regression Model

For 12-week total symptom burden, age, income, employment status, ethnicity, drinking status, exercise program type, exercise adherence, number of co-morbidities, and cancer type had p-values <0.2 in the univariable analysis (Table 3.4) and were included in the first multivariable regression model. The final model included baseline total symptom score, adherence, number of co-morbidities, program type, age, and sex. Higher baseline scores and two or more co-morbidities were both associated with higher (worse) 12-week total symptom scores while higher adherence, and in-person exercise programs were associated with lower (better) 12-week scores. Age and sex were controlled for in the model (Table 3.5). No evidence of multicollinearity was found. R^2 and adjusted R^2 were 0.48 and 0.47, respectively. The standard error of the regression estimate was 8.8. A scatterplot of the model residuals can be found in Figure 3.2.

Table 3.5: Multivariable regression model for total symptom burden

12-week Total Symptom Burden					
	Coefficient	**Standard Error of Coefficient**	**95% CI of Coefficient**	**Standardized Coefficient**	**p-value**
Constant	15.309	3.442	8.537-22.080		
Baseline total symptom score	0.655	0.043	0.571-0.739	0.634	**<0.001**
Adherence (%)	-0.077	0.025	-0.126- -0.028	-0.127	**0.002**
Two+ co-morbidities	2.722	1.044	0.668-4.777	0.109	**0.010**
In-person program	-2.947	1.188	-5.283- -0.610	-0.101	**0.014**
Age	-0.046	0.035	-0.115-0.023	-0.056	0.192
Female	-0.062	0.987	-2.004-1.880	-0.003	0.950

Statistically significant (p <0.05)

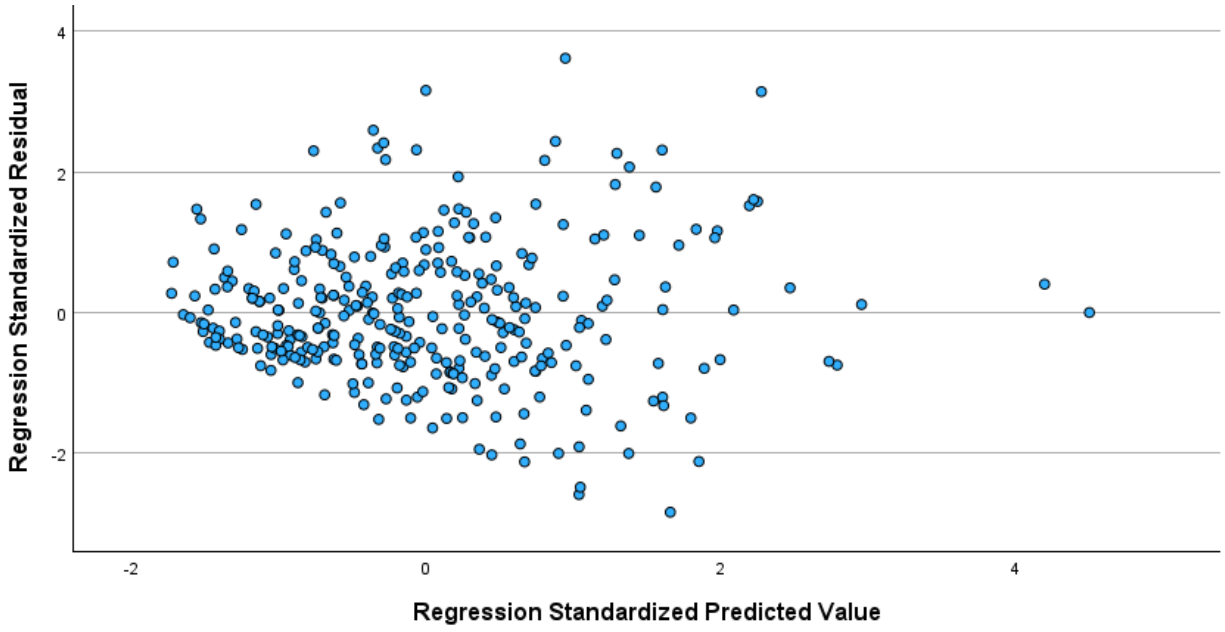

Figure 3.2: Scatterplot of linear regression model residuals

Discussion

The primary objective of this study was to evaluate the effectiveness of the 12-week ACE program on symptom burden in individuals with hematological cancers. Our findings support the benefit of exercise for ESAS-r physical symptom score, tiredness, and drowsiness ($p < 0.05$); but not for the ESAS-r total symptom score. While statistically significant, the estimated mean effect sizes for fatigue and drowsiness of 0.15 and 0.13 respectively were smaller than the mean standardized effect size for fatigue previously reported in a meta-analysis of aerobic exercise for individuals with hematological cancers (ES 0.31; CI: 0.13, 0.48) (Knips et al., 2019). The smaller effect sizes found in our study may be due to the lack of a control group comparison, and the high percent of participants who were on systemic therapy (45%) at the time of the intervention. Of note, the mean effect size for participants who had completed cancer therapy was 0.20 for tiredness, an estimate that falls within the confidence interval reported in the meta-analysis by Knips et al., (Knips et al., 2019). Due to the overall low baseline scores in our sample, these findings may only be valid in individuals with low symptom burden on entry into an exercise program, although no cut-points for low and high symptom burden have been established for the ESAS-r summary scores.

Participants who were on systemic therapy during the intervention improved less than those who were not on systemic therapy. However, a lack of improvement does not mean that these participants did not benefit from the exercise program (Schmitz et al., 2015). Previous research shows that exercising during cancer treatment can mitigate treatment-related symptoms, particularly fatigue (Haines et al., 2010; Mijwel et al., 2019; Ndjavera et al., 2020; Schmidt et al., 2015; van Waart et al., 2015); although most of this research has been conducted in women with breast cancer. One RCT examining aerobic exercise for individuals with lymphoma (both on and

off treatment), reported the benefits of exercise during chemotherapy treatment consisted of both preventing declines and actual gains in functioning, whereas the benefits for participants who were off-treatment consisted entirely of gains in physical functioning (Courneya et al., 2009). Our analysis showed similar findings, with mean physical and total symptom scores improving in both on and off treatment groups with larger improvements seen in participants who were off treatment. These findings support an important potential benefit of exercise in attenuating declines in physical symptoms during systemic cancer treatments.

There were no significant differences for total symptom burden at either time point between males and females. This contradicts previous studies in multiple myeloma where females were found to have higher symptom burden than males (Campagnaro et al., 2008; Kamal et al., 2021). Biological sex was included in our regression models to control for known and unknown factors related this variable, but it was not significant in any of our models. Participants in the ACE program expressed gender identities that were the same as their assigned biological sex at birth (cisgender). Thus, although gender was a variable of consideration for the analyses, it was not included in our models and we are unable to make conclusions about potential gender differences. Having two or more co-morbidities was associated with higher total symptom burden which aligns with previous research on symptom burden in individuals with various cancers (Bubis et al., 2018; Shi et al., 2011). Ethnicity was not included in any of our final models; however, our sample was 76% white and non-white participants had non-significantly ($p > 0.05$) higher baseline and 12-week total symptom burden scores. Our sample may not have had enough ethnic diversity to detect differences.

Higher adherence was significantly associated with lower 12-week scores on total symptom burden. Overall adherence was 76%, which is higher than the mean rate of 63.7%

reported in a recent systematic review of exercise implementation studies in cancer (Czosnek et al., 2021) as well as higher than the reported mean rate of 65% in a systematic review and meta analysis of RCTs of aerobic exercise programs in cancer (Bullard et al., 2019). The ACE study attrition rate of 8% was also better than the range of 22% to 56% reported across other implementation studies (Czosnek et al., 2021).

In-person exercise was significantly associated with lower (better) 12-week total symptom burden scores when compared to virtual exercise. While baseline scores were similar across both groups; significant improvements in symptoms were found only for participants taking part in-person. Previous research shows that virtual exercise oncology programs are feasible (Myers et al., 2022; Purdy, Venner, et al., 2022; Sattar et al., 2021) and may be beneficial for various outcomes including physical functioning (Myers et al., 2022), fatigue (Myers et al., 2022; Wonders et al., 2021), physical symptom burden (Purdy, Venner, et al., 2022) and quality of life (Wonders et al., 2021). While in ACE, virtual exercise programs appeared to be less effective for symptoms than in-person programs, virtual programs are an alternative for people who are unable to access in-person programs or who would prefer participating from home, although further large scale trials are needed (Gonzalo-Encabo et al., 2022).

The ESAS was originally developed for individuals with advanced cancers in palliative care (Bruera et al., 1991). Most of the psychometric research for the ESAS-r has been done in samples of patients with advanced cancer and/or in palliative care settings (Nekolaichuk et al., 2008; Watanabe et al., 2011, 2012) and therefore, the ESAS-r may not be appropriate for use in patients with early stage cancer. As well, the tiredness and drowsiness items of the ESAS-r may not adequately measure cancer-related fatigue. A systematic review of 154 qualitative research articles on cancer-related fatigue described differences in how individuals with cancer perceive

tiredness versus fatigue, demonstrating that fatigue is conceptually distinct from tiredness in individuals with cancer (Scott et al., 2011).

Limitations

This is a secondary analysis of an implementation study in real-world settings with no comparison group. As a result, we are unable to distinguish between the effect of the intervention, a placebo effect, and the effect of time. Because the analysis is limited to adults with hematological cancer, the findings may not be generalizable to children nor other adult cancer populations. As we performed a post-hoc secondary analysis, not all potentially relevant determinants of symptom burden, such as data on recent blood cell counts, were available. Furthermore, both total and physical symptom burden scores were low in this sample, and thus, the findings may not be valid in individuals with higher symptom scores.

Conclusions

Much of the literature on exercise in hematological cancers focuses on HRQL, individual symptoms, physical functioning, and fitness outcomes. To our knowledge, this is the first study to examine the effects of a community-based exercise program on symptom burden in individuals with hematological cancer. Our finding suggest that exercise is more beneficial for physical symptoms than total symptom burden. Symptom scores tended to decrease with age, and no significant differences were found for total or physical symptom burden at either time point between males and females. Our findings identified potential determinants of post-intervention symptom burden scores that require further prospective investigation prior to being used to inform clinical practice.

CHAPTER 4: DISCUSSION

There is a large body of evidence demonstrating that exercise and physical activity are safe and beneficial for most individuals with cancer (Campbell et al., 2019; Stout et al., 2017). Despite this, exercise is often not a part of standard cancer care (Kennedy et al., 2022) and few individuals with cancer report meeting physical activity recommendations (Blanchard et al., 2008; Stevinson et al., 2014). Many barriers to implementing exercise in standard practice have been identified. At the organizational level, barriers relate to lack of capacity, staff, resources (including space and equipment), and standard referral pathways (Kennedy et al., 2022). At government and economic levels, the lack of a reimbursement structure for exercise, and policies directing the inclusion of exercise into standard care have been identified as barriers (Kennedy et al., 2022).

A scoping review of implementation studies of exercise oncology programs found that most programs were funded through research grants or foundation funds. To ensure long-term maintenance of programs, sustainable funding through the health system or health insurance plans is required, which would require decision-maker buy-in (Purdy, Sobierajski, et al., 2022). Systematic reviews have demonstrated that exercise oncology programs can be cost-effective (Gubler-Gut et al., 2021; Khan et al., 2019; Wang et al., 2023); however, there is a large amount of variability in results of individual studies, likely due in part to variability in exercise parameters, settings, and patient characteristics between studies. The majority of economic evaluations of exercise oncology programs include cost-utility evaluations utilizing QALYs derived from the EQ-5D, which is the most commonly used generic utility measure (Gubler-Gut et al., 2021; Khan et al., 2019; Wang et al., 2023). Economic evidence supporting the cost-

benefit of exercise may be helpful for persuading decision-makers at both the organizational and government levels to direct more resources to exercise oncology programs.

While using a single metric that can compare the cost-effectiveness of different interventions across patient groups may be attractive to decisions-makers, generic utility measures are limited in that they often do not measure specific aspects of HRQL that are important to certain patient groups. Specifically, the EQ-5D does not measure energy or fatigue, which is a common and impactful symptom reported by individuals with cancer (Teckle et al., 2011). To best estimate the benefit of exercise, other outcomes such as physical activity behaviour, quality of life and symptoms need to be considered.

An additional barrier to implementation of exercise programming is the lack of a clinical care pathway for decision-making relative to exercise services for individuals undergoing or recovering from cancer. Identifying the characteristics of individuals who are more likely to benefit from a structured exercise program can help inform care and referral to programming. Offering a range of program options, such as clinic-based individualized exercise and community-based group exercise, and matching participants to the most appropriate location and supervision level may make programs more inclusive and accessible (Purdy, Sobierajski, et al., 2022). Moreover, targeting individuals who are likely to benefit the most from a structured exercise program may be helpful if resources are limited.

Limitations

A limitation of our analysis was the focus on improvement in symptom burden as an outcome. For many individuals with cancer, preventing declines in symptoms is beneficial and there is evidence that exercise is effective for mitigating treatment related declines, particularly for fatigue (Courneya et al., 2009; Haines et al., 2010; Mijwel et al., 2019; Ndjavera et al., 2020;

Schmidt et al., 2015; van Waart et al., 2015). As ESAS-r scores are collected at clinical visits within Cancer Care Alberta, the opportunity exists for future analyses involving matching samples of individuals who did not participate in ACE.

Mean baseline symptom scores were low in our sample. This may be because individuals with higher symptom burden may not have felt well enough to participate in an exercise program. For these individuals, referral to supportive care interventions such as physical or occupational therapy or psycho-social interventions to address their most distressing symptoms may be more appropriate, as a first step, than referral to community-based exercise.

This analysis was limited to people choosing to participate in a community-based exercise program; however, 29% were insufficiently active and 56% were sedentary at baseline, indicating a desire for cancer-specific exercise programming among individuals who were not already active. The findings are also limited to adults with hematological and are not generalizable to other cancer populations. However, effects of exercise on symptom burden, and the determinants of symptom burden and change in symptom likely differ between cancer types, and as such, we decided to focus our analysis on hematological cancers. Furthermore, individuals with hematological cancer are underrepresented in the current exercise oncology literature—literature dominated by breast cancer studies.

Further limitations are related to medical data. Information about cancer stage was inconsistently reported and not available for all participants. Furthermore, for participants who had completed treatment, we were unable to determine how long after treatment completion they joined ACE. Individuals were eligible to join ACE up to three years after completing treatment and may respond differently to exercise in the period of time immediately after completing treatment (i.e. first year) versus a longer time interval (i.e. two to three years).

Regression analysis has its limitations. It is sensitive to multicollinearity. Although VIF scores and correlations indicated there was no evidence of multicollinearity in our models, there may be some overlap between variables, as age and the number of co-morbidities, and employment status are correlated. The presence of heteroscedasticity and outliers also affect a model's validity and precision. However, in our models, standard errors of the coefficients tended to be small and confidence intervals were narrow, indicating that the variables included in our models were reasonably precise.

Conclusions and future directions

This thesis addressed two components that are relevant to implementation of exercise oncology programs in clinical practice: cost-effectiveness and symptom burden. Chapter 2 identified gaps in the current economic literature and made recommendations for future studies to better facilitate economic evaluations. This included better reporting of data related to generic utility measures, consideration of cancer recurrence and mortality over longer time horizons and considering the results of CUAs in the context of other study outcomes. Chapter 3 evaluated the effectiveness of the exercise programs on symptom burden and identified potential determinants associated with post-intervention symptom burden in individuals with hematological cancers that should be further investigated in future research. Establishing the economic evidence and the creation of referral pathways are necessary components to bridge the gap between research and practice, and support the implementation of exercise programs for individuals with cancer. Future exercise oncology research is needed addressing one or more of these components.

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APPENDICES

Appendix A: ESAS-r

Alberta Health Services

Affix patient label within this box

Edmonton Symptom Assessment System Revised (ESAS-r)

Please circle the number that best describes how you feel NOW:

No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Pain
No Tiredness *(Tiredness = lack of energy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Tiredness
No Drowsiness *(Drowsiness = feeling sleepy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Drowsiness
No Nausea	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Nausea
No Lack of Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Lack of Appetitie
No Shortness of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Shortness of Breath
No Depression *(Depression = feeling sad)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Depression
No Anxiety *(Anxiety = feeling nervous)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Anxiety
Best Wellbeing *(Wellbeing = how you feel overall)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Wellbeing
No _____ Other Problem *(For example constipation)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible _____

Appendix B: Godin-Shepherd Leisure-Time Physical Activity Questionnaire

We would like you to recall your average weekly exercise over the past month. How many times per week on average did you do the following kinds of exercise over the past month?

When answering these questions please remember to: Consider your average weekly exercise over the past month Only count exercise sessions that lasted 15 minutes or longer in duration Only count exercise that was done during free time (i.e. do not included occupation or housework) Note the main difference between the three categories is the intensity of the exercise Write the average frequency on the first line and the average duration on the second line

STRENUOUS EXERCISE (Heart beats rapidly, sweating) (e.g., running, jogging, hockey, soccer, squash, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling, vigorous aerobic dance classes, heavy weight training).

In an average week I was involved in strenuous exercise _____ times/week for an average duration of _____ minutes/each session.

MODERATE EXERCISE (Not exhausting, light perspiration) (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing).

In an average week I was involved in moderate exercise _____ times/week for an average duration of _____ minutes/each session.

MILD EXERCISE (Minimal effort, no perspiration) (e.g., easy walking, yoga, archery, fishing, bowling, lawn bowling, shuffleboard, horseshoes, golf, snowmobiling).

In an average week I was involved in mild exercise _____ times/week for an average duration of _____ minutes/each session.

RESISTANCE TRAINING EXERCISE (e.g. exercises with dumbbells, body weight, bands, such as squats, bicep curls, etc.).

In an average week I perform resistance training activities_____ times/ week for an average duration of _____ minutes/session.

FLEXIBILITY TRAINING EXERCISE (e.g. yoga, stretching)

In an average week I perform flexibility training activities_____ times/ week for an average duration of _____ minutes/session.

Appendix C: Medical data abstraction form

Study ID: _____ Initials: _____ Date: _____

1. Date of initial diagnosis of cancer: _____ (DD/MM/YYYY)
2. Type of cancer: _____

Staging

Multiple Myeloma:

- ISS stage: _____
- CA by iFISH: _____
- LDH: _____
- Overall stage: _____

Lymphoma

- B-cell NHL Type:

  - indolent

  - aggressive

- T-cell NHL (T-cell and NK-cell)

  -Systemic

  -Primary Cutaneous

- Hodgkin Type: - Classical Hodgkin lymphoma/

  -Nodular lymphocyte-predominant Hodgkin lymphoma

  - Stage I, II, III, IV: Limited or Advanced Stage

  -Subtype A – Asymptomatic

  -SubtypeB – Constitutional symptoms: fever, night sweats, or weight loss >10% of baseline

Leukemia:

Type: CLL, CML, ALL, AML, Hairy Cell Leukemia

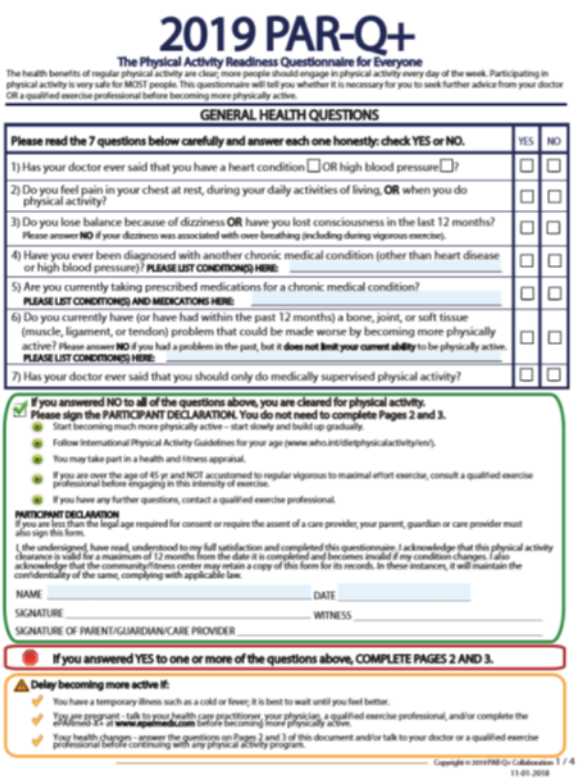
Staging: Chronic leukemias: low risk (Stage 0); intermediate risk (Stage 1 and II); high risk (Stage III and IV)

AML: untreated, active disease, in remission, measurable residual disease, relapsed or refractory.

ALL: untreated, in remission, relapsed or refractory

HCL: symptom-based – no staging

Appendix D : PAR-Q+



2019 PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

The health benefits of regular physical activity are clear; more people should engage in physical activity every day of the week. Participating in physical activity is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

GENERAL HEALTH QUESTIONS

Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	YES	NO
1) Has your doctor ever said that you have a heart condition ☐ OR high blood pressure ☐?	☐	☐
2) Do you feel pain in your chest at rest, during your daily activities of living, **OR** when you do physical activity?	☐	☐
3) Do you lose balance because of dizziness **OR** have you lost consciousness in the last 12 months? Please answer **NO** if your dizziness was associated with over-breathing (including during vigorous exercise).	☐	☐
4) Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)? **PLEASE LIST CONDITION(S) HERE:**	☐	☐
5) Are you currently taking prescribed medications for a chronic medical condition? **PLEASE LIST CONDITION(S) AND MEDICATIONS HERE:**	☐	☐
6) Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Please answer **NO** if you had a problem in the past, but it **does not limit your current ability** to be physically active. **PLEASE LIST CONDITION(S) HERE:**	☐	☐
7) Has your doctor ever said that you should only do medically supervised physical activity?	☐	☐

If you answered NO to all of the questions above, you are cleared for physical activity.
Please sign the PARTICIPANT DECLARATION. You do not need to complete Pages 2 and 3.

- Start becoming much more physically active – start slowly and build up gradually.
- Follow International Physical Activity Guidelines for your age (www.who.int/dietphysicalactivity/en/).
- You may take part in a health and fitness appraisal.
- If you are over the age of 45 yr and NOT accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.
- If you have any further questions, contact a qualified exercise professional.

PARTICIPANT DECLARATION

If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that the community/fitness center may retain a copy of this form for its records. In these instances, it will maintain the confidentiality of the same, complying with applicable law.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

If you answered YES to one or more of the questions above, COMPLETE PAGES 2 AND 3.

Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ at **www.eparmedx.com** before becoming more physically active.
- Your health changes - answer the questions on Pages 2 and 3 of this document and/or talk to your doctor or a qualified exercise professional before continuing with any physical activity program.

11-01-2018

2019 PAR-Q+

FOLLOW-UP QUESTIONS ABOUT YOUR MEDICAL CONDITION(S)

1. Do you have Arthritis, Osteoporosis, or Back Problems?
If the above condition(s) is/are present, answer questions 1a-1c — If **NO** ☐ go to question 2

1a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatment(s)) YES ☐ NO ☐

1b. Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)? YES ☐ NO ☐

1c. Have you had steroid injections or taken steroid tablets regularly for more than 3 months? YES ☐ NO ☐

2. Do you currently have Cancer of any kind?
If the above condition(s) is/are present, answer questions 2a-2b — If **NO** ☐ go to question 3

2a. Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and/or neck? YES ☐ NO ☐

2b. Are you currently receiving cancer therapy (such as chemotherapy or radiotherapy)? YES ☐ NO ☐

3. Do you have a Heart or Cardiovascular Condition? This Includes Coronary Artery Disease, Heart Failure, Diagnosed Abnormality of Heart Rhythm
If the above condition(s) is/are present, answer questions 3a-3d — If **NO** ☐ go to question 4

3a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments) YES ☐ NO ☐

3b. Do you have an irregular heart beat that requires medical management? (e.g., atrial fibrillation, premature ventricular contraction) YES ☐ NO ☐

3c. Do you have chronic heart failure? YES ☐ NO ☐

3d. Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months? YES ☐ NO ☐

4. Do you have High Blood Pressure?
If the above condition(s) is/are present, answer questions 4a-4b — If **NO** ☐ go to question 5

4a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments) YES ☐ NO ☐

4b. Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer **YES** if you do not know your resting blood pressure) YES ☐ NO ☐

5. Do you have any Metabolic Conditions? This Includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes
If the above condition(s) is/are present, answer questions 5a-5e — If **NO** ☐ go to question 6

5a. Do you often have difficulty controlling your blood sugar levels with foods, medications, or other physician-prescribed therapies? YES ☐ NO ☐

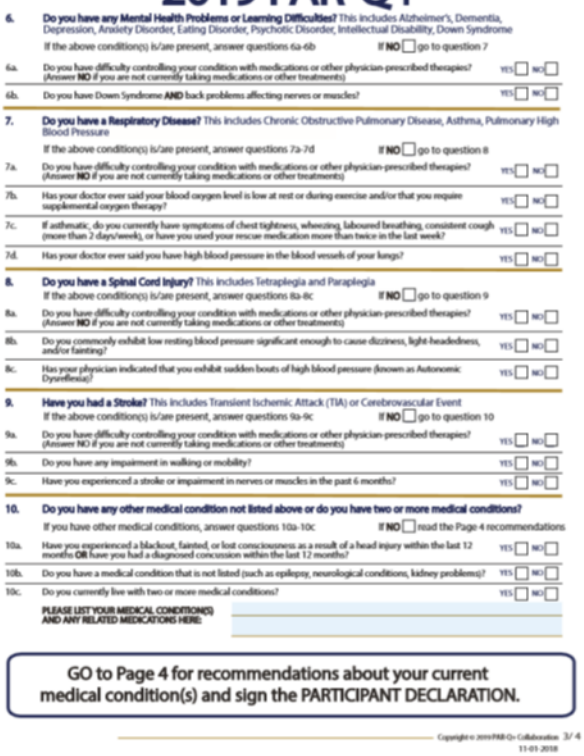
5b. Do you often suffer from signs and symptoms of low blood sugar (hypoglycemia) following exercise and/or during activities of daily living? Signs of hypoglycemia may include shakiness, nervousness, unusual irritability, abnormal sweating, dizziness or light-headedness, mental confusion, difficulty speaking, weakness, or sleepiness. YES ☐ NO ☐

5c. Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, **OR** the sensation in your toes and feet? YES ☐ NO ☐

5d. Do you have other metabolic conditions (such as current pregnancy-related diabetes, chronic kidney disease, or liver problems)? YES ☐ NO ☐

5e. Are you planning to engage in what for you is unusually high (or vigorous) intensity exercise in the near future? YES ☐ NO ☐

11-01-2018



2019 PAR-Q+

6. Do you have any Mental Health Problems or Learning Difficulties? This includes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome
If the above condition(s) is/are present, answer questions 6a-6b — If **NO** ☐ go to question 7

6a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments) YES ☐ NO ☐

6b. Do you have Down Syndrome **AND** back problems affecting nerves or muscles? YES ☐ NO ☐

7. Do you have a Respiratory Disease? This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure
If the above condition(s) is/are present, answer questions 7a-7d — If **NO** ☐ go to question 8

7a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments) YES ☐ NO ☐

7b. Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy? YES ☐ NO ☐

7c. If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week? YES ☐ NO ☐

7d. Has your doctor ever said you have high blood pressure in the blood vessels of your lungs? YES ☐ NO ☐

8. Do you have a Spinal Cord Injury? This includes Tetraplegia and Paraplegia
If the above condition(s) is/are present, answer questions 8a-8c — If **NO** ☐ go to question 9

8a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments) YES ☐ NO ☐

8b. Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting? YES ☐ NO ☐

8c. Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)? YES ☐ NO ☐

9. Have you had a Stroke? This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event
If the above condition(s) is/are present, answer questions 9a-9c — If **NO** ☐ go to question 10

9a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments) YES ☐ NO ☐

9b. Do you have any impairment in walking or mobility? YES ☐ NO ☐

9c. Have you experienced a stroke or impairment in nerves or muscles in the past 6 months? YES ☐ NO ☐

10. Do you have any other medical condition not listed above or do you have two or more medical conditions?
If you have other medical conditions, answer questions 10a-10c — If **NO** ☐ read the Page 4 recommendations

10a. Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months **OR** have you had a diagnosed concussion within the last 12 months? YES ☐ NO ☐

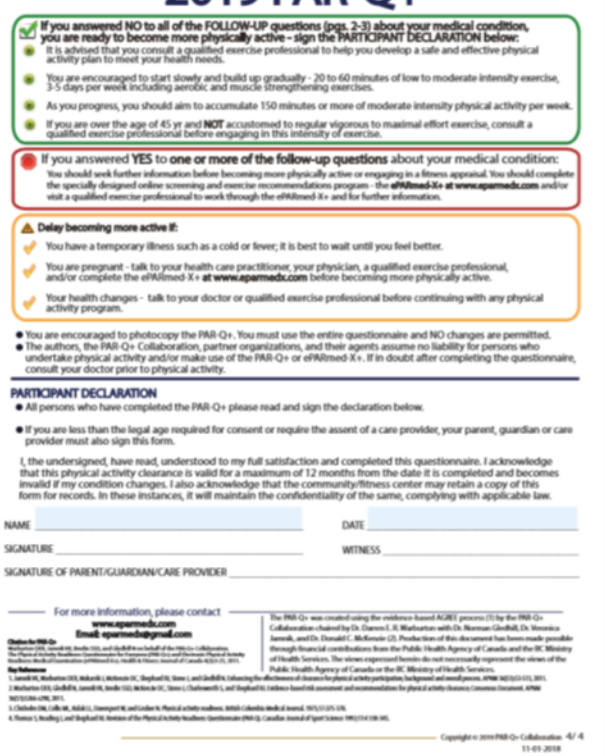
10b. Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)? YES ☐ NO ☐

10c. Do you currently live with two or more medical conditions? YES ☐ NO ☐

PLEASE LIST YOUR MEDICAL CONDITION(S) AND ANY RELATED MEDICATIONS HERE: _____

GO to Page 4 for recommendations about your current medical condition(s) and sign the PARTICIPANT DECLARATION.

11-01-2018



2019 PAR-Q+

If you answered NO to all of the FOLLOW-UP questions (pgs. 2-3) about your medical condition, you are ready to become more physically active – sign the PARTICIPANT DECLARATION below:

- It is advised that you consult a qualified exercise professional to help you develop a safe and effective physical activity plan to meet your health needs.
- You are encouraged to start slowly and build up gradually - 20 to 60 minutes of low to moderate intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.
- As you progress, you should aim to accumulate 150 minutes or more of moderate intensity physical activity per week.
- If you are over the age of 45 yr and **NOT** accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.

If you answered YES to one or more of the follow-up questions about your medical condition:
You should seek further information before becoming more physically active or engaging in a fitness appraisal. You should complete the specially designed online screening and exercise recommendations program - the **ePARmed-X+ at www.eparmedx.com** and/or visit a qualified exercise professional to work through the ePARmed-X+ and for further information.

Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ **at www.eparmedx.com** before becoming more physically active.
- Your health changes - talk to your doctor or qualified exercise professional before continuing with any physical activity program.

- You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
- The authors, the PAR-Q+ Collaboration, partner organizations, and their agents assume no liability for persons who undertake physical activity and/or make use of the PAR-Q+ or ePARmed-X+. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.

PARTICIPANT DECLARATION

- All persons who have completed the PAR-Q+ please read and sign the declaration below.
- If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that the community/fitness center may retain a copy of this form for records. In these instances, it will maintain the confidentiality of the same, complying with applicable law.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

For more information, please contact
www.eparmedx.com
Email: eparmedx@gmail.com

The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+ Collaboration chaired by Dr. Darren E. R. Warburton with Dr. Norman Gledhill, Dr. Veronica Jamnik, and Dr. Donald C. McKenzie (2). Production of this document has been made possible through financial contributions from the Public Health Agency of Canada and the BC Ministry of Health Services. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada or the BC Ministry of Health Services.

11-01-2018