Longitudinal Physical Activity Patterns and Accumulation of Chronic Conditions in Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study

Investigators

Name	Institute	Email
Lauren Appell	Arkansas Children's Hospital; University of Arkansas for Medical Sciences	leappell@uams.edu
Deo Kumar Srivastaava	St Jude Children's Research Hospital	Kumar.srivastava@stjude.org
Grace Zhou	St Jude Children's Research Hospital	Grace.Zhou@STJUDE.ORG
Kiri Ness	St Jude Children's Research Hospital	Kiri.ness@stjude.org
Tara Brinkman	St Jude Children's Research Hospital	Tara.brinkman@stjude.org
Kevin Krull	St Jude Children's Research Hospital	Kevin.krull@stjude.org
Eric Chow	Fred Hutchinson Cancer Center	ericchow@uw.edu
Kevin Oeffinger	Duke	kevin.oeffinger@duke.edu
Claire Synder	Johns Hopkins University	csnyder@jhu.edu
Paul Nathan	Hospital for Sick Children	Paul.nathan@sickkids.ca
Greg Armstrong	St Jude Children's Research Hospital	Greg.armstrong@stjude.org
Rebecca Howell	MD Anderson Cancer Center	rhowell@mdanderson.org
Ellen van der Plas	Arkansas Children's Hospital; University of Arkansas for Medical Sciences	evanderplas@uams.edu

Working Groups

- Primary: Chronic Disease
- Secondary:
    - Psychology/Neuropsychology
    - Cancer Control

Background

Survival after childhood cancer now exceeds 85%, with over 520,000 living survivors of childhood cancer in the United States.[1,2] With mounting evidence of premature onset and accelerated accumulation of chronic health conditions and physiologic decline, survivorship comes at a high cost for survivors and society.[3,4] A recent report from the Childhood Cancer Survivor Study (CCSS) used the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) and demonstrated that survivors have both a higher and more rapidly increasing chronic condition burden than siblings, indicating accelerated biological aging.[5] Chronic conditions—spanning cardiovascular, metabolic, endocrine, and neurologic systems—represent a leading cause of morbidity, reduced quality of life, and early mortality among survivors.[6–8] Because past treatment exposures in survivors of childhood cancer cannot be undone, there is a dire need to identify modifiable behavioral factors that mitigate this burden to promote healthy survivorship. Physical inactivity is one such factor.

In the general population, regular moderate-to-vigorous physical activity (PA) reduces cardiovascular and metabolic disease risk and all-cause mortality, whereas sedentary behavior independently predicts adverse outcomes.[9–11] However, most childhood cancer survivors fail to achieve guideline-recommended activity levels: In CCSS, only 46% of survivors met Center for Disease Control and Prevention recommendations, with lower

PA among those with musculoskeletal or neurologic conditions or relapse.[12,13] Data from activity trackers confirm that adult survivors of childhood acute lymphoblastic leukemia (ALL) are significantly more sedentary than healthy peers.[14] These behaviors appear early in survivorship, with fatigue, neuropathy, and fear of injury being most commonly cited as barriers to exercise.[12]

The physiologic consequences of inactivity are striking. In cross-sectional analyses of the St. Jude Lifetime Cohort (SJLIFE), Ness et al. first characterized frailty in young adult survivors, defined by exhaustion, weakness, and low activity, at rates comparable to individuals over 65 years old.[8] Hayek et al. later confirmed with the CCSS cohort that frailty prevalence was three times higher in survivors than siblings and that sedentary lifestyle, smoking, and obesity mediated treatment-related risk.[6] Longitudinal analyses using the SJLIFE cohort show that frailty prevalence doubled starting five years post-diagnosis, with sedentary lifestyle and lack of resistance training among the strongest modifiable predictors.[15] Chua et al. demonstrated that physical inactivity is often the earliest manifestation of frailty—a condition that is present in nearly 40% of ALL survivors in their twenties—underscoring its potential as a sentinel biomarker of physiologic decline.[16]

Moreover, the relationship between PA and chronic condition burden is unlikely to be uniform across all survivors. In another CCSS study, Hudson et. al. showed that cancer diagnosis type determines the constellation of treatment-related sequelae — CNS tumor survivors face motor, coordination, and neurocognitive deficits that constrain physical activity capacity, while bone tumor survivors report the highest rates of adverse health status among all diagnostic groups.[17] Treatment intensity further shapes long-term vulnerability in regards to chronic health: survivors exposed to anthracyclines and chest radiation carry elevated cardiovascular risk, while those treated with cranial radiation face neuroendocrine and neurocognitive dysfunction that may independently limit PA engagement.[10,18] A recent CCSS analysis demonstrated that population attributable fractions for unhealthy lifestyle (including physical inactivity, smoking, obesity, and alcohol use) exceeded those of chemotherapy and radiotherapy for multiple chronic conditions, including hypertension, diabetes, and impaired quality of life.[19] Further, lifestyle factors are associated with cardiovascular risk factor profiles independent of both genetic predisposition and treatment exposures.[20,21] Despite this evidence, no study has formally evaluated whether diagnosis type, treatment intensity, or co-occurring lifestyle risk behaviors moderate the longitudinal association between PA trajectories and chronic condition burden.

Beyond treatment and lifestyle factors, neurocognitive and psychological characteristics may shape a survivor's capacity to engage in and benefit from PA. Low PA is associated with a 4.5-fold increased risk of global neurocognitive impairment in survivors, and those with cognitive deficits may face barriers to both planning and sustaining exercise.[18,22,23] Psychological distress is associated with lower odds of meeting PA recommendations and greater engagement in health-risking behaviors.[24,25] Notably, perceived physical and mental health status — rather than chronic conditions alone — directly predicts PA levels in childhood cancer survivors.[26,27] Despite this evidence, no study has evaluated whether these factors moderate the longitudinal PA–chronic condition burden relationship.

Exercise and rehabilitation interventions have shown efficacy in mitigating these deficits. Systematic reviews indicate that structured physical training improves strength, aerobic capacity, and quality of life in children and adolescents with ALL.[28,29] Meta-analyses confirm exercise safety and feasibility during and after treatment[28] and recent reviews emphasize the need for early, sustained programs to preserve cardiorespiratory fitness.[30] Fitness itself strongly predicts long-term health outcomes: in large survivorship cohorts, lower peak oxygen uptake and muscle strength correlate with greater disease burden and reduced health-related quality of life.[31] In an analysis of 2,500 survivors, Mayr et al. demonstrated that higher physical fitness was inversely associated with clinically assessed disease burden, suggesting that cardiorespiratory fitness mediates the relationship between activity and chronic morbidity.[31]

Despite this growing evidence, critical knowledge gaps remain. Existing studies are primarily cross-sectional or conducted at a single-institution, and rarely evaluate how *changes* in physical activity (PA) affect chronic disease trajectories over time. With the combination of a large cohort of childhood cancer survivors, repeated assessments of PA, chronic health conditions and indices of frailty and chronic condition burden, CCSS offers a unique opportunity to quantify how lifestyle patterns shape the trajectory of chronic condition accumulation.

Understanding these dynamics could inform risk-stratified survivorship guidelines and intervention trials aimed at promoting physical activity as a cornerstone of lifelong health after childhood cancer.

Specific Aims

Aim 1: Impact of physical activity trajectories on changes in chronic condition burden

Aim 1a: Determine whether physical activity trajectories between follow-up (FU) 5 and FU7--as defined by published guidelines (≥9 MET-hours/week)--are associated with subsequent changes in chronic condition burden between FU5 and FU8, as measured by the CIRS-G.
Hypothesis 1a: Compared with the persistently active group or sustained activity groups, individuals who are persistently inactive or report declining physical activity trajectory will exhibit a significantly greater increase (worsening) in CIRS-G total scores from FU5 to FU8, after adjusting for baseline CIRS-G T-scores at FU5.
Aim 1b: Determine if there is a dose-response relationship between continuous changes in physical activity (MET-hours/week) from FU5 to FU7 with changes in chronic condition burden (CIRS-G scores) from FU5 to FU8.
Hypothesis 1b: Greater increases in physical activity (per 1 MET increase) from FU5 to FU7 will be independently associated with a greater decrease in chronic condition burden (lower CIRS-G scores) from FU5 to FU8.

Aim 2: Diagnosis, treatment, and lifestyle moderators of the association between physical activity and changes chronic condition burden

Aim 2a: Evaluate whether cancer diagnosis type (e.g., CNS vs. non-CNS) modifies the association between changes in PA in METs from FU5 to FU7 and changes in chronic condition burden from FU5 to FU8, as measured by the CIRS-G.
Hypothesis 2a: The adverse impact of declining activity/persistent inactivity from FU5 to FU7 will be associated with an exacerbated increase in chronic condition burden among CNS and bone tumor survivors due physical limitations.
Aim 2b: Assess whether demographic (age, sex, race/ethnicity) and treatment intensity (e.g., surgery along/minimal localized therapy; chemotherapy alone; multimodal therapy [chemotherapy and radiation]; high-dose therapy)) modify the association between changes in PA from FU5 to FU7 (METs) and changes in chronic condition burden from FU5 to FU8.
Hypothesis 2b: Treatment intensity and female sex will moderate the association between declines in PA from FU5 to FU7 (i.e., lower METs) and changes in chronic condition burden. For example, the association between declining PA (FU5–FU7) and increased chronic condition burden will be exacerbated in females and survivors exposed to high-intensity treatment regimens.
Aim 2c: Determine if lifestyle factors (e.g., smoking, risky alcohol intake) and/or body mass index moderate the relationship between PA and chronic health condition burden.
Hypothesis 2c: The protective association between increased physical activity (FU5–FU7) and a greater decrease (improvement) or stabilization in chronic condition burden from FU5 to FU8 will be significantly attenuated in survivors who smoke, engage in risky drinking, or meet criteria for obesity at baseline.

Aim 3: Neurocognitive and psychological moderators of the physical activity-cumulative chronic condition burden relationship

Aim 3a: Evaluate whether neurocognitive impairment at FU5 affects the relationship between changes in physical activity from FU5 to FU7 and subsequent changes in chronic condition burden from FU5 to FU8, as measured by the CIRS-G.
Hypothesis 3a: Neurocognitive impairment at FU5 will attenuate the impact of physical activity on chronic condition burden trajectories. Specifically, survivors with neurocognitive impairment will exhibit a significantly weaker association between changes in physical activity (FU5–FU7) and subsequent changes in CIRS-G T-scores from FU5 to FU8, compared to those without impairment.
Aim 3b: Evaluate whether psychological distress at FU5 affects the relationship between changes in physical activity from FU5 to FU7 and subsequent chronic condition burden (CIRS-G) at FU8.

Hypothesis 3b: Elevated psychological distress (anxiety/depression) at FU5 will moderate the relationship between physical activity change and health outcomes, with high-distress survivors experiencing less reduction in chronic condition burden from increased PA.

Aim 3c: Evaluate whether health-related quality of life (HRQOL) at FU5 affects the relationship between changes in physical activity from FU5 to FU7 and subsequent changes in chronic condition burden from FU5 to FU8, as measured by the CIRS-G.

Hypothesis 3c: The protective effect of increasing physical activity (FU5–FU7) on subsequent changes in chronic condition burden from FU5 to FU8 will be significantly diminished in survivors reporting low baseline HRQOL at FU5 compared to those with high HRQOL, who will show a greater decrease (improvement) or stabilization in CIRS-G T-scores.

Methods

Synopsis

The proposed study population will include survivors from the original and expansion cohorts of CCSS who completed physical activity assessments at FU5 and FU7 (to calculate changes in metabolic equivalents [METS]) and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) assessment at FU5 and FU8.

Study Population

Inclusion criteria:

- CCSS survivors
- Completion of PA assessments at FU5 and FU7
- Completion of CIRS-G at FU5 and FU8

Exclusion criteria:

- Missing key exposure or outcome data
- Relapse or second malignancy prior to FU5 assessment window (sensitivity analysis will evaluate inclusion)

Primary Outcome: Chronic Condition Burden (CIRS-G)

The primary outcome variable will be chronic health condition burden, measured using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). The CIRS-G rates impairment across 14 organ systems on a 0–4 scale, where higher scores represent greater severity.

- Total burden: sum across 14 organ systems (overall primary outcome variable)
- Total organ system categories endorsed: count of how many of the 14 organ systems receive a score >0 (ranging from 0-14)
- Severity index: total score divided by the number of categories endorsed (average score of the affected system); gauges intensity of a survivors' chronic condition burden
- Number of categories at grade 3 or 4: count of how many organ system scored are graded ≥3 (severe/constant disability) or a 4 (extremely severe/organ failure)
- Number of categories at grade 4: count of how many systems scored at a grade 4; life-threatening burden.

Availability of CIRS-G scores at FU5 and FU8

As described in detail by Esbenshade and colleagues[1] CIRS-G scores at FU5 were derived from a grading rubric mapped to the International Classification of Disease (ICD)-9 and 10 codes. This rubric classifies participant reported conditions where a physician provided a diagnosis or where the participant reported taking a condition-specific medication (see also concept 15-01). In their 2023 paper, the authors establish five CIRS-G metrics derived from FU5 data: (1) total score; (2) total organ system categories endorsed (3) severity index; (4) number of organ system categories at grade 3 or 4; and (5) number of categories at grade 4. Identical CIRS-G coding protocols were applied to the most recent FU8 survey data, allowing us to compute the continuous T-score change metrics proposed in this application.

Primary Predictor: Physical Activity

Physical activity will be assessed using self-reported items from the CCSS follow-up questionnaires, which capture the frequency and duration of vigorous and moderate-to-vigorous physical activity (MVPA). These data will be converted to Metabolic Equivalent (MET)-hours per week based on standard Compendium values.

- Continuous Variable: Total volume of physical activity expressed as MET-hours/week.
- Binary Variable: Adherence to CDC/ACSM guidelines, defined as meeting MET-hours/week (equivalent to ≥150 minutes/week of moderate-intensity activity).
- Change (FU5 to FU7): Categorized as
    - Persistently Active: met guidelines (9 MET-hours/week) at both FU5 and FU7
    - Increased Activity: did not meet guidelines at FU5, but did meet guidelines at FU7
    - Persistently Inactive: did not meet guidelines at FU5 and FU7
    - Decreased Activity: did meet guidelines at FU5, but did not meet guidelines at FU7
- Longitudinal Patterns: Classification of activity trajectories as sustained, intermittent, or declining throughout the study duration.

We will examine the distribution of survivors across the four physical activity change categories to determine if the sample size is sufficient to consider all categories of change. If needed, we will combine the persistently active and increased activity groups, and the persistently inactive and decreased activity groups.

Covariates

<u>Demographics at FU5</u>:

- Age (continuous variable)
- Sex
    - Male
    - Female
- Race/ethnicity
    - Non-Hispanic-White
    - Non-Hispanic -Black
    - Hispanic
    - Other
- Education
    - ≥College
    - <College
- Insurance
    - Public
    - Private
    - Other
- Marital status
    - Never married
    - Married/living with partner
    - Widowed/divorced/separated

<u>Treatment-intensity</u>

Treatment-intensity risk groups will be adapted from the BCCSS risk stratification framework[32], modified to incorporate detailed treatment exposures available in the CCSS cohort. This stratification has been previously utilized in other CCSS studies.[33] Note: radiation therapy is abbreviated XRT.

Risk Stratum	Diagnosis	Treatment-based Risk Stratification within CCSS	Frobisher et. al.
Low	ALL	Chemo only with Doxorubicin Equivalent Dose ≤ 100 mg/m^2	No XRT
	Wilms tumor	No XRT No anthracyclines	No XRT No chemotherapy
	Non-CNS tumor	Surgery only	Surgery only
Medium	Non-CNS tumors	Anyone not in Low or High Risk	Non-Hodgkin lymphoma (NHL) with chemo or XRT
			Hodgkin lymphoma with chemo only
			ALL with >0 Gy but <24 Gy cranial XRT
			Wilms/Bone/NBL/STS with Chemotherapy or Radiation but not Both
	CNS tumors	No XRT	No XRT
High	Any	Cranial Radiation Therapy ≥ 24Gy	(ALL only) Cranial Radiation Therapy ≥ 24Gy
		Autologous or Allogeneic Transplant	(ALL only) Autologous or Allogeneic Transplant
		Direct Radiation Therapy to neck, chest, abdomen, or pelvis	Hodgkin lymphoma with XRT
		Cyclophosphamide Equivalent Dose ≥10 g/m2; Cisplatin >400 mg/m^2, Doxorubicin Equivalent Dose ≥ 250 mg/m^2	Wilms/Bone/NBL/STS with Chemotherapy and XRT
	CNS tumors	Any XRT	Any XRT

*Note that Frobisher non-CNS tumor diagnoses do not include AML/other leukemias, which they classified as Medium risk if they received chemotherapy or radiation. CCSS would stratify these into high or medium risk as shown.

**This table has been adopted from a previous CCSS study.[33]

Lifestyle factors/Body Mass Index in FU5:

- Smoking:
  - Ever smoked (“yes” 100 cigarettes, “no” smoke now)
  - Currently smoke (“yes” 100 cigarettes, “yes” smoke now)
  - Never smoke (“no” 100 cigarettes, “no” smoke now)
  - Smoking status will be assessed in models as current/ever vs. never
- Alcohol use:
  - Heavy drinking (operationalized as ≥5 drinks/day for women and ≥6 drinks/day for men at least once/month for the past year)
  - Risky drinking (>3 drinks/day or 7 drinks/week for women, and >4 drinks/day or 14 drinks/week for men)
  - No alcohol use
- Body Mass Index
  - ≥30 (obese)
  - <30 (not-obese)

Emotional distress, quality of life and neurocognitive function:

- *CCSS Neurocognitive Questionnaire (NCQ)*[34]: The NCQ is a 25-item self-report tool for neurocognitive functioning. Standardized Z-scores across four domains (task efficiency, emotion regulation, organization

and memory) will be evaluated. Impairment will be defined as a Z-score ≥1.33, representing a score above the 90th percentile of the sibling sample.

- *The Brief Symptom Inventory (BSI-18)*[35]: The BSI-18 is a self-report questionnaire specifically designed to screen for psychological distress symptoms experienced in the previous seven days, including somatization, depression, anxiety and an overall measure of psychological distress (Global Severity Index). T-scores ≥ 63 are considered clinically elevated and indicative of emotional distress.
- *Health-related quality of life (HRQOL):* We will assess HRQOL with the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), which asks about one's health and functioning over the past four weeks. The SF-36 includes subscales measuring physical functioning, role functioning due to physical problems, bodily pain, general health perceptions, vitality, role functioning due to emotional problems, social functioning, and mental health. Primary analyses will focus on the two summary scales derived from the SF-36, including the physical component summary and the mental component summary. Since physical functions are highly relevant to someone's ability to exercise, we will also conduct models on each of the subscales. Scores for each item are reported as T-scores, with lower scores representing worse HRQOL. Poor HRQOL is defined as T-scores ≤40.

Statistical Framework

Descriptive Analyses

- Summarize cohort characteristics by physical activity trajectories (see Table 1).

Aim 1: Changes in physical activity and changes in cumulative chronic condition burden

Aim 1a: Determine whether physical activity trajectories between follow-up (FU) 5 and FU7--as defined by published guidelines (≥9 MET-hours/week)--are associated with subsequent changes in chronic condition burden between FU5 and FU8, as measured by the CIRS-G.

1. Multivariable linear regression (Table 2):
    - Outcome: Change in chronic condition burden (ΔCIRS-G = FU8 CIRS-G − FU5 CIRS-G)
    - Categorical predictor:
        - Persistently Active: met guidelines (9 MET-hours/week) at both FU5 and FU7
        - Increased Activity: did not meet guidelines at FU5, but did meet guidelines at FU7
        - Decreased Activity: did meet guidelines at FU5, but did not meet guidelines at FU7
        - Persistently Inactive (Reference): did not meet guidelines at FU5 and FU7
    - Covariates (determined at FU5): CIRS-G, MET at FU5, age, sex, race/ethnicity, education, insurance status
2. Multinomial Logistic regression (Table 3):
    - Outcome: Change in severity of chronic condition burden
        - Consistently low chronic condition burden (Severity level does not exceed a Grade 1 rating; T-score remains within 1SD at FU5 and FU8)
        - Consistently high chronic condition burden (Severity level is ≥2; T scores remain within 1SD at FU5 and FU8)
        - Reduced chronic condition burden (T-score declines ≤1SD from FU5 to FU8)
        - Increased chronic condition burden (T-scores increases ≤1SD from FU5 to FU8)
    - Categorical predictor:
        - Persistently Active: met guidelines (≥9 MET-hours/week) at both FU5 and FU7
        - Increased Activity: did not meet guidelines at FU5, but did meet guidelines at FU7
        - Decreased Activity: met guidelines at FU5 but not at FU7
        - Persistently Inactive (Reference): did not meet guidelines at either time point
    - Covariates: CIRS-G at FU5, MET at FU5, demographics at FU5 (age, sex, race/ethnicity, education, insurance)

Aim 1b: Determine if there is a dose-response relationship between continuous changes in physical activity (MET-hours/week) from FU5 to FU7 with changes in chronic condition burden (CIRS-G scores) from FU5 to FU8.

1. Multivariable linear regression (Table 4):
    - Outcome: Change in CIRS-G total score from FU5 to FU8
    - Primary predictor: change in METs from FU5 to FU7 (primary analysis)
    - Covariates (determined at FU5): CIRS-G, demographics at FU5 (age, sex, race/ethnicity, education, insurance), MET

Aim 2: Moderators of the association between physical activity and changes in chronic condition burden

Aim 2a: Evaluate whether cancer diagnosis type (e.g., CNS vs. non-CNS) modifies the association between changes in PA in METs from FU5 to FU7 and changes in chronic condition burden from FU5 to FU8, as measured by the CIRS-G.
Aim 2b: Assess whether demographic (age, sex, race/ethnicity) and treatment intensity (e.g., surgery alone/minimal localized therapy; chemotherapy alone; multimodal therapy [chemotherapy and radiation]; high-dose chemotherapy/radiation, stem-cell transplantation) modify the association between changes in PA from FU5 to FU7 (METs) and changes in chronic condition burden from FU5 to FU8.
Aim 2c: Determine if lifestyle factors (e.g., smoking, risky alcohol intake) and/or body mass index moderate the relationship between PA and chronic health condition burden

1. Multivariable linear regression
    - Primary outcome: Change in chronic condition burden (ΔCIRS-G = FU8 CIRS-G − FU5 CIRS-G)
    - Primary predictor (aim 2a/2b): ΔMET-hours/week (FU5 to FU7)
    - Moderators (interaction terms with ΔMET-hours/week):
        - Aim 2a (Table 5): Diagnosis Type: Categorical (CNS vs Non-CNS).
        - Aim 2b (Table 6): Models will first be stratified by sex (M or F), then within each sex stratum, the interaction between ΔMET-hours/week and treatment intensity will be tested
        - Aim 2c: Lifestyle factors at FU5:
            a. Smoking (no vs. yes; Table 7)
            b. Risky drinking (no vs. yes; Table 8)
            c. Obesity (no vs. yes; Table 9)
    - Covariates (determined at FU5): CIRS-G score; MET; Demographics: Age, Sex, and Race/Ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Other).

Aim 3: Neurocognitive and psychological moderators of the physical activity-cumulative chronic condition burden relationship

Aim 3a: Evaluate whether neurocognitive impairment at FU5 affects the relationship between changes in physical activity from FU5 to FU7 and subsequent changes in chronic condition burden from FU5 to FU8, as measured by the CIRS-G.
Aim 3b: Evaluate whether psychological distress at FU5 affects the relationship between changes in physical activity from FU5 to FU7 and subsequent chronic condition burden (CIRS-G) from FU5 to FU8.
Aim 3c: Evaluate whether health-related quality of life (HRQOL) at FU5 affects the relationship between changes in physical activity from FU5 to FU7 and subsequent changes in chronic condition burden from FU5 to FU8, as measured by the CIRS-G.

1. Multivariable linear regression
    - Primary Outcome: Change in chronic condition burden (ΔCIRS-G = FU8 CIRS-G − FU5 CIRS-G)
    - Predictors:
        - ΔMET-hours/week (FU5 to FU7)
    - Moderators (interaction terms with ΔMET-hours/week):

- Aim 3a: Categorical neurocognitive predictor (separate models for each domain) at FU5 (e.g., PA*Task Efficiency impairment [yes/no]; Table 10)
- Aim 3b:Categorical emotional distress predictor (separate models for each domain) at FU5 (e.g., PA*Anxiety [yes/no]; Table 11)
- Aim 3c: Categorical predictor (not impaired vs. impaired) for physical component summary score /mental component summary scores (separate models; Tables 12, 13) at FU5 (e.g., PA*HRQOL impairment [yes/no]; Table 9)
    - Models with each of the 8 subscale scores will be conducted to explore specificity of the relationship between HRQOL, physical activity and cumulative chronic illness burden

- Covariates (determined at FU5): CIRS-G, MET, Demographics (age, sex, race/ethnicity),

Potential pitfalls and mitigation strategies

A primary methodological concern is 'reverse causality', i.e., survivors with a higher baseline chronic condition burden may have functional limitations that restrict their ability to engage in physical activity. While the observational nature of these data restricts causal inference to the determination of longitudinal associations, we account for this potential confounding in two ways.

First, all statistical models will control for baseline chronic condition burden at FU5 as a covariate. Second, our temporal design establishes clear chronological precedence: while physical activity trajectories are assessed from FU5 to FU7, the primary outcome of chronic condition burden is captured across a longer timeframe from FU5 to FU8. This specific timeframe was selected because the interval between FU7 and FU8 alone (~4–5 years) may be insufficient to capture meaningful, detectable changes in chronic condition burden. Evaluating the outcome through FU8 ensures adequate latency for physical activity behavior to manifest as shifts in health trajectories, while guaranteeing that the behavioral exposure strictly precedes the downstream changes in condition burden.

Scientific Impact

This study will define how changes in physical activity influence the accumulation of chronic health conditions in childhood cancer survivors, a critical and unresolved question in survivorship research. By identifying physical activity as a modifiable determinant of multisystem morbidity, this work will inform risk-stratified survivorship care and provide a strong rationale for targeted lifestyle interventions to mitigate long-term disease burden.

Tables

Table 1 Demographics

		Physical Activity Trajectories from FU5 to FU7				
	Total Sample	**Persistently Active**	**Increased Activity**	**Persistently Inactive**	**Decreased Activity**	**P-value**
Sex						
Male (N, %)						
Female (N, %)						
Age at FU5						
Mean (SD)						
Median (min, max)						
Race/Ethnicity						
NH-White (N, %)						
NH-Black (N, %)						
Hispanic (N, %)						
Other (N, %)						
Annual household income at FU5						
≤$19,000 (N, %)						
$20,000-$39,999 (N, %)						
$40,000-$59,000 (N, %)						
≥$60,000 (N, %)						
Insurance status at FU5						
Public (N, %)						
Private (N, %)						
Other (N, %)						
Marital/Relationship status						
Never married						
Married/living with partner						
Widowed/divorced/separated						
Educational attainment						
<College						
≥College						
Time from FU5 to FU7 (years)						
Mean (SD)						
Smoking status						
Never (N, %)						
Former/Current (N, %)						
Alcohol consumption						
Heavy (N, %)						
Risky (N, %)						
None (N, %)						
Body Mass Index						
Not obese (N, %)						
Obese (N, %)						
Age at cancer diagnosis (years)						
Mean (SD)						
Median (min, max)						
Cancer diagnosis						
ALL (N, %)						
CNS malignancy (N, %)						
Hodgkin lymphoma (N, %)						
Neuroblastoma (N, %)						
Wilms tumor (N, %)						
Soft tissue sarcoma (N, %)						
Osteosarcoma (N, %)						
Other bone tumors (N, %)						
Surgery						
Yes (N, %)						

No (N, %)				
Antimetabolite chemotherapy				
Yes (N, %)				
No (N, %)				
Anthracyclines				
Yes (N, %)				
No (N, %)				
Alkylating agents				
Yes (N, %)				
No (N, %)				
Corticosteroids				
Yes (N, %)				
No (N, %)				
Radiation				
Yes (N, %)				
No (N, %)				
Cranial radiation				
None/Scatter (≤Gy)				
>2Gy to <20 Gy				
≥20 Gy				

Table 2: Multivariable linear regression. Outcome: Change in CIRS-G Total Score from FU5 to FU8

Variables	**β**	**95% CI**	**p-value**
ΔMET-hours/week (FU5 to FU7)			
Persistently Active	Reference	-	-
Increased activity			
Persistently Inactive			
Decreased Activity			
Covariates at FU5			
CIRS-G Total Score			
Physical Activity (MET-hour/week)			
Age (years)			
Sex			
Male	Reference	-	-
Female			
Race/ethnicity			
NH-White	Reference	-	-
NH-Black			
Hispanic			
Other			
Education			
≥College	Reference	-	-
<College			
Insurance			
Public	Reference	-	-
Private			
Other			

Table 3: Multinomial logistic regression. Outcome: Change in severity of chronic condition burden

	Change in Chronic Condition Burden FU5-FU8					
	Reduced Burden vs. Consistently Low Burden		**Increased Burden vs. Consistently Low Burden**		**Consistently High Burden vs. Consistently Low Burden**	
Variables	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
MET-hours/week (FU5 to FU7)						
Persistently Active	1.00 (Ref)	-	1.00 (Ref)	-	1.00 (Ref)	-
Increased Activity						
Persistently Inactive						
Decreased Activity						
Covariates (at FU5)						
CIRS-G Total Score						
Physical Activity (MET-hour/week)						
Age (years)						
Sex						
Male	1.00 (Ref)	-	1.00 (Ref)	-	1.00 (Ref)	-
Female						
Race/ethnicity						
NH-White	1.00 (Ref)	-	1.00 (Ref)	-	1.00 (Ref)	-
NH-Black						
Hispanic						
Other						
Education						
≥College	1.00 (Ref)	-	1.00 (Ref)	-	1.00 (Ref)	-
<College						
Insurance						
Public	1.00 (Ref)	-	1.00 (Ref)	-	1.00 (Ref)	-
Private						
Other						

Table 4. Dose-Response Relationship Between Change in MET-Hours/Week and Chronic Condition Burden. Outcome: Change in CIRS-G Total Score from FU5 to FU8

Variables	**β**	**95% CI**	**p-value**
Change in MET-hours/week (FU5 to FU7; continuous variable)			
Covariates at FU5			
CIRS-G Total Score			
Physical Activity (MET-hour/week)			
Age (years)			
Sex			
Male	Reference	-	-
Female			
Race/ethnicity			
NH-White	Reference	-	-
NH-Black			
Hispanic			
Other			
Education			
≥College	Reference	-	-
<College			
Insurance			
Public	Reference	-	-
Private			
Other			

Table 5. Aim 2a: Moderation of Physical Activity Change and Chronic Condition Burden by Diagnosis Type. Outcome: Change in CIRS-G Total Score from FU5 to FU8

Variables	**β**	**95% CI**	**p-value**
Change in MET-hours/week (FU5 to FU7; continuous variable)			
Diagnosis type			
Non-CNS	Reference	-	-
CNS			
Interaction terms (moderation)			
ΔMET × CNS			
Covariates at FU5			
CIRS-G Total Score			
Physical Activity (MET-hour/week)			
Age (years)			
Sex			
Male	Reference	-	-
Female			
Race/ethnicity			
NH-White	Reference	-	-
NH-Black			
Hispanic			

Other			
Education			
≥College	Reference	-	-
<College			
Insurance			
Public	Reference	-	-
Private			
Other			

Table 6. Aim 2b: Moderation by Treatment-Intensity. Outcome: Change in CIRS-G Total Score from FU5 to FU8

Variables	**β**	**95% CI**	**p-value**
ΔMET-hours/week (FU5 to FU7)			
Treatment intensity			
Level 1 (minimal)	Reference	-	-
Level 2 (Moderate)			
Level 3 (High intensity)			
Level 4 (Most aggressive)			
Interaction			
MET x Moderate			
MET x High intensity			
MET x Most aggressive			
Covariates at FU5			
CIRS-G Total Score			
Physical Activity (MET-hour/week)			
Age (years)			
Sex			
Male	Reference	-	-
Female			
Race/ethnicity			
NH-White	Reference	-	-
NH-Black			
Hispanic			
Other			
Education			
≥College	Reference	-	-
<College			
Insurance			
Public	Reference	-	-
Private			
Other			

Table 7. Aim 2C: Moderation by Lifestyle Factors (Smoking). Outcome: Change in CIRS-G Total Score from FU5 to FU8

Variables	**β**	**95% CI**	**p-value**
ΔMET-hours/week (FU5 to FU7)			
Smoking at FU5			
Never	Reference	-	-
Former/Current			
Interaction			
MET x Smoking (Former/Current)	-	-	-
Covariates at FU5			
CIRS-G Total Score			
Physical Activity (MET-hour/week)			
Age (years)			
Sex			
Male	Reference	-	-
Female			
Race/ethnicity			
NH-White	Reference	-	-
NH-Black			
Hispanic			
Other			
Education			
≥College	Reference	-	-
<College			
Insurance			
Public	Reference	-	-
Private			
Other			

Table 8. Aim 2C: Moderation by Lifestyle Factors (Risky Drinking). Outcome: Change in CIRS-G Total Score from FU5 to FU8

Variables	**β**	**95% CI**	**p-value**
ΔMET-hours/week (FU5 to FU7)			
Alcohol Consumption at FU5			
No	Reference	-	-
Risky			
Heavy			
Interaction			
MET x Alcohol (Risky)	-	-	-
MET x Alcohol (Heavy)	-	-	-
Covariates at FU5			
CIRS-G Total Score			
Physical Activity (MET-hour/week)			
Age (years)			
Sex			
Male	Reference	-	-

Female			
Race/ethnicity			
NH-White	Reference	-	-
NH-Black			
Hispanic			
Other			
Education			
≥College	Reference	-	-
<College			
Insurance			
Public	Reference	-	-
Private			
Other			

Table 9. Aim 2C: Moderation by Lifestyle Factors (Obesity). Outcome: Change in CIRS-G Total Score from FU5 to FU8

Variables	**β**	**95% CI**	**p-value**
ΔMET-hours/week (FU5 to FU7)			
Obesity at FU5			
No	Reference	-	-
Yes			
Interaction			
MET x Obesity	-	-	-
Covariates at FU5			
CIRS-G Score			
Physical Activity (MET-hour/week)			
Age (years)			
Sex			
Male	Reference	-	-
Female			
Race/ethnicity			
NH-White	Reference	-	-
NH-Black			
Hispanic			
Other			
Education			
≥College	Reference	-	-
<College			
Insurance			
Public	Reference	-	-
Private			
Other			

Table 10 Aim 3a: Moderation by Neurocognitive Impairment (Example: Task Efficiency). Change in CIRS-G Total Score from FU5 to FU8

Note that similar models will be run for other domains of the NCQ, i.e., Memory, Organization, and Emotion Regulation

Variables	**β**	**95% CI**	**p-value**
ΔMET-hours/week (FU5 to FU7)			
Task Efficiency Impairment at FU5			
No	Reference	-	-
Yes			
Interaction Term			
ΔMET * Task Efficiency Impairment at FU5			
Covariates at FU5			
CIRS-G Total Score			
Physical Activity (MET-hour/week)			
Age (years)			
Sex			
Male	Reference	-	-
Female			
Race/ethnicity			
NH-White	Reference	-	-
NH-Black			
Hispanic			
Other			
Education			
≥College			
<College			
Insurance			
Public			
Private			
Other			

Table 11 aim 3b: Moderation by Psychological Distress (Example: Anxiety). Outcome: Change in CIRS-G Total Score from FU5 to FU8.

Note that similar models will be run for other domains of the BSI-18, i.e., Depression and Global Severity Index

Variables	**β**	**95% CI**	**p-value**
ΔMET-hours/week (FU5 to FU7)			
Anxiety at FU5			
No	Reference	-	-
Yes			
Interaction Term			
ΔMET * Anxiety at FU5			

Covariates at FU5			
CIRS-G Total Score			
Physical Activity (MET-hour/week)			
Age (years)			
Sex			
Male	Reference	-	-
Female			
Race/ethnicity			
NH-White	Reference	-	-
NH-Black			
Hispanic			
Other			
Education			
≥College			
<College			
Insurance			
Public			
Private			
Other			

Table 12. Aim 3c: Moderation by Health-Related Quality of Life (HRQOL) Physical Component Summary (PCS) Score. Outcome: Change in CIRS-G Total Score from FU5 to FU8

Variables	**β**	**95% CI**	**p-value**
ΔMET-hours/week (FU5 to FU7)			
PCS Impairment at FU5			
No	Reference	-	-
Yes			
Interaction Term			
ΔMET * PCS Impairment at FU5			
Covariates at FU5			
CIRS-G Total Score			
Physical Activity (MET-hour/week)			
Age (years)			
Sex			
Male	Reference	-	-
Female			
Race/ethnicity			
NH-White	Reference	-	-
NH-Black			
Hispanic			
Other			
Education			
≥College			
<College			

Insurance			
Public			
Private			
Other			

Table 13. Aim 3c: Moderation by Health-Related Quality of Life (HRQOL) Mental Component Summary (MCS) Score. Outcome: Change in CIRS-G Total Score from FU5 to FU8

Variables	**β**	**95% CI**	**p-value**
ΔMET-hours/week (FU5 to FU7)			
MCS Impairment at FU5			
No	Reference	-	-
Yes			
Interaction Term			
ΔMET * MCS Impairment at FU5			
Covariates at FU5			
CIRS-G Total Score			
Physical Activity (MET-hour/week)			
Age (years)			
Sex			
Male	Reference	-	-
Female			
Race/ethnicity			
NH-White	Reference	-	-
NH-Black			
Hispanic			
Other			
Education			
≥College			
<College			
Insurance			
Public			
Private			
Other			

Note that similar models will be run separately for the remaining eight domain scores of the SF-36 to explore potential specificity of the impact of physical and mental HRQOL on physical activity and cumulative chronic condition burden.

References

1. Institute, N. C. Childhood Cancer Survivor Study: An Overview. https://www.cancer.gov/types/childhood-cancers/ccss.

2. Institute, N. C. NCCR*Explorer: An interactive website for NCCR cancer statistics [Internet]. https://nccrexplorer.ccdi.cancer.gov.

3. Nipp, R. D. *et al.* Financial Burden in Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. *J. Clin. Oncol.* **35**, JCO.2016.71.706 (2017).

4. Nathan, P. C., Henderson, T. O., Kirchhoff, A. C., Park, E. R. & Yabroff, K. R. Financial Hardship and the Economic Effect of Childhood Cancer Survivorship. *J Clin Oncol* **36**, 2198–2205 (2018).

5. Esbenshade, A. J. *et al.* Accumulation of Chronic Disease Among Survivors of Childhood Cancer Predicts Early Mortality. *J. Clin. Oncol.* **41**, 3629–3641 (2023).

6. Hayek, S. *et al.* Prevalence and Predictors of Frailty in Childhood Cancer Survivors and Siblings: A Report From the Childhood Cancer Survivor Study. *J. Clin. Oncol.* **38**, 232–247 (2020).

7. Delaney, A. *et al.* Progression of Frailty in Survivors of Childhood Cancer: A St. Jude Lifetime Cohort Report. *JNCI: J. Natl. Cancer Inst.* **113**, 1415–1421 (2021).

8. Ness, K. K. *et al.* Frailty in childhood cancer survivors. *Cancer* **121**, 1540–1547 (2015).

9. Rock, C. L. *et al.* American Cancer Society nutrition and physical activity guideline for cancer survivors. *CA: A Cancer J. Clin.* **72**, 230–262 (2022).

10. Ryan, T. D. *et al.* Cardiovascular Toxicity in Patients Treated for Childhood Cancer: A Scientific Statement From the American Heart Association. *Circulation* **151**, e926–e943 (2025).

11. Schindera, C. *et al.* Physical activity and screen time in children who survived cancer: A report from the Swiss Childhood Cancer Survivor Study. *Pediatr. Blood Cancer* **67**, e28046 (2020).

12. Mizrahi, D. *et al.* Barriers and enablers to physical activity and aerobic fitness deficits among childhood cancer survivors. *Pediatr. Blood Cancer* **67**, e28339 (2020).

13. Ness, K. K. *et al.* Predictors of inactive lifestyle among adult survivors of childhood cancer. *Cancer* **115**, 1984–1994 (2009).

14. Vyhlídal, T., Dygrýn, J., Hrubá, J. & Chmelík, F. Accelerometry-based assessment of physical activity and sedentary behavior in adult survivors of childhood acute lymphoblastic leukemia and their healthy peers. *Sci. Rep.* **13**, 7439 (2023).

15. Webster, R. T. *et al.* Health behavior profiles in young survivors of childhood cancer: Findings from the St. Jude Lifetime Cohort Study. *Cancer* **129**, 2075–2083 (2023).

16. Chua, L. L., Azanan, M. S., Oh, L. & Ariffin, H. Physical Inactivity as an Early Sign of Frailty in Young Adult Survivors of Childhood Acute Lymphoblastic Leukemia. *J. Pediatr. Hematol.Oncol.* **45**, e560–e566 (2023).

17. Hudson, M. M. *et al.* Health Status of Adult Long-term Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. *JAMA* **290**, 1583–1592 (2003).

18. Banerjee, P. *et al.* Using neurocognitive phenotypes to inform interventions for adult survivors of childhood cancer. *JNCI: J. Natl. Cancer Inst.* **116**, 1856–1866 (2024).

19. Onerup, A. *et al.* Potential for risk reduction of chronic health conditions through lifestyle in childhood cancer survivors. *Nat. Commun.* **17**, 4605 (2026).

20. Wilson, C. L. *et al.* Influence of treatment, genetic predisposition, and lifestyle on cardiovascular risk factors among cancer survivors. *JNCI: J. Natl. Cancer Inst.* **118**, 711–720 (2025).

21. Bouwman, E. *et al.* Unhealthy lifestyle behaviors, overweight, and obesity among childhood cancer survivors in the Netherlands: A DCCSS LATER study. *Cancer* **130**, 2856–2872 (2024).

22. Ness, K. K. *et al.* Mapping aging phenotypes in childhood cancer survivors: A report from the St. Jude Lifetime Cohort. *J. Clin. Oncol.* **42**, 10069–10069 (2024).

23. Semendric, I. *et al.* Prevalence of cancer-related cognitive impairment in pediatric patients and survivors of non-CNS cancers: A systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* **176**, 106283 (2025).

24. Hudson, M. M. *et al.* Long-term Follow-up Care for Childhood, Adolescent, and Young Adult Cancer Survivors. *Pediatrics* **148**, e2021053127 (2021).

25. Miller, N. E. *et al.* Psychological distress and health behaviours in people living with and beyond cancer: a cross-sectional study. *Sci. Rep.* **14**, 15367 (2024).

26. Janardan, S. K., Lewis, R. W., Marchak, J. G., Mertens, A. C. & Effinger, K. E. The association of perceived health status and presence of chronic conditions with physical activity in childhood cancer survivors. *Support. Care Cancer* **33**, 98 (2025).

27. Pradhan, K. R. *et al.* Endocrine and Metabolic Disorders in Survivors of Childhood Cancers and Health-Related Quality of Life and Physical Activity. *J. Clin. Endocrinol. Metab.* **104**, 5183–5194 (2019).

28. Simioni, C. *et al.* Physical training interventions for children and teenagers affected by acute lymphoblastic leukemia and related treatment impairments. *Oncotarget* **9**, 17199–17209 (2018).

29. Coombs, A., Schilperoort, H. & Sargent, B. The effect of exercise and motor interventions on physical activity and motor outcomes during and after medical intervention for children and adolescents with acute lymphoblastic leukemia: A systematic review. *Crit. Rev. Oncol.Hematol.* **152**, 103004 (2020).

30. Lemay, V. *et al.* Prevention of Long-term Adverse Health Outcomes With Cardiorespiratory Fitness and Physical Activity in Childhood Acute Lymphoblastic Leukemia Survivors. *J. Pediatr. Hematol.Oncol.* **41**, e450–e458 (2018).

31. Mayr, A. K. *et al.* Physical fitness and clinically assessed disease burden in long-term childhood cancer survivors—The SURfit study. *Cancer* **131**, e70051 (2025).

32. Frobisher, C. *et al.* Risk stratification of childhood cancer survivors necessary for evidence-based clinical long-term follow-up. *Br. J. Cancer* **117**, 1723–1731 (2017).

33. Dinan, M. A. *et al.* Treatment exposure-based risk-stratification for care of survivors of childhood cancer: a report from the childhood cancer survivor study. *JNCI: J. Natl. Cancer Inst.* **117**, 2580–2590 (2025).

34. Kenzik, K. M. *et al.* The Childhood Cancer Survivor Study–Neurocognitive Questionnaire (CCSS-NCQ) Revised: Item Response Analysis and Concurrent Validity. *Neuropsychology* **29**, 31–44 (2015).

35. Recklitis, C. J., Blackmon, J. E. & Chang, G. Validity of the Brief Symptom Inventory-18 (BSI-18) for Identifying Depression and Anxiety in Young Adult Cancer Survivors: Comparison With a Structured Clinical Diagnostic Interview. *Psychol. Assess.* **29**, 1189–1200 (2017).