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ORIGINAL ARTICLE

Effect of a 1-year physical activity intervention on quality of life, fatigue, and distress in adult childhood cancer survivors—A randomized controlled trial (SURfit)

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Abstract

Introduction: Childhood cancer survivors (CCS) are at risk of experiencing lower quality-of-life, fatigue, and depression. Few randomized controlled trials have studied the effect of physical activity (PA) on these in adult long-term CCS. This study investigated the effect of a 1-year individualized PA intervention on health-related quality-of-life (HRQOL), fatigue, and distress symptoms in adult CCS.

Methods: The SURfit trial randomized 151 CCS ≥16 years old, <16 at diagnosis and ≥5 years since diagnosis, identified through the Swiss Childhood Cancer Registry. Intervention participants received personalized PA counselling to increase intense PA by ≥2.5 h/week for 1 year. Controls maintained usual PA levels. The authors assessed physical- and mental-HRQOL, fatigue, and distress symptoms at baseline, 3, 6, and 12 months. T-scores were calculated using representative normative populations (mean = 50, standard deviation = 10). Generalized linear mixed-effects models with intention-to-treat (ITT, primary), and three per-protocol allocations were used.

The last three authors contributed equally to this article.

The clinical trial registration is Clinicaltrials.gov identifier: NCT02730767.

Results: At 12 months, ITT (−3.56 larger decrease, 95% confidence interval −5.69 to −1.43, $p = .001$) and two per-protocol analyses found significantly lower fatigue. Physical-HRQOL improved significantly in two per-protocol analyses at 12 months. No other effects were found.

Conclusion: SURfit showed that increased intense PA over 1 year improved fatigue in adult CCS. Survivors should be recommended PA to reduce the burden of late-effects.

KEYWORDS
childhood cancer survivors, late effects, mental health, physical activity, randomized controlled trial

INTRODUCTION

Around 96% of childhood cancer survivors (CCS) suffer from a chronic health condition by age 45.[1,2] These include psychological distress symptoms,[3–5] fatigue,[6,7] and reduced health-related quality-of-life (HRQOL), hereafter named psychosocial outcomes.[3,8–10] Physical activity (PA) is a known modifiable health behavior that can prevent and improve these late-effects in adult cancer survivors.[11] Recent research, however, suggests CCS are not active enough over the course of their lives.[12,13] Providing multimodal PA interventions have been found effective in increasing PA among CCS.[14,15]

High-quality randomized controlled trials (RCTs) on PA are still rare in long-term CCS[16] with only eight RCTs on PA interventions and psychosocial outcomes.[17-25] PA was found to improve HRQOL in three of seven studies,[17–24] one study found reduced negative mood,[25] and one found reduced fatigue whereas the other showed no effect.[19,22,26] The majority included survivors 1–2 years post-treatment, only one included adult CCS,[22] and none intervened for more than 6 months. Long-term CCS may respond differently to PA interventions as short-term treatment related side effects are cleared, and the cumulative burden of modifiable late-effects steadily increases with time after cancer.[2]

The objective of this RCT was to evaluate the effect of a 1-year individualized PA intervention on HRQOL, fatigue, and distress symptoms in adult CCS, defined as secondary end points of the SURfit trial.[27] In a post hoc subgroup analysis, we aimed to investigate whether the intervention effect differed between participants with low versus high levels of each respective outcome at baseline.

MATERIALS AND METHODS

This article is written in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[28]

Trial design and participants

The SURfit study (https://ClinicalTrials.gov/study/NCT02730767) was a single-center, parallel armed, 1:1 superiority RCT. Eligible participants were identified through the Swiss Childhood Cancer Registry,[27] and included CCS <16 years old at diagnosis, diagnosed according to the International Classification of Childhood Cancer[29] or with Langerhans cell histiocytosis, diagnosed and/or treated at a clinic of the Swiss Paediatric Oncology Group, ≥5 years since last cancer diagnosis, and ≥16 years old at enrollment. We aimed to include a general population of CCS to increase external validity of this trial. Written informed consent and approval from the Ethics Committee of Northwest and Central Switzerland (BASEC-ID: 2019-00410) was obtained before conducting the study from 2015 to 2019.

In the current article, we investigated the intervention effect on pre-specified secondary outcomes of the SURfit study: HRQOL, fatigue, and distress symptoms. The primary outcome of the SURfit study was change in a composite cardiovascular disease risk score.[27] The protocol pre-specified the separate publication of three groups of outcomes: cardiovascular disease risk (primary),[30] bone health (secondary),[31] and psychosocial health (current article, secondary). Full study protocol, publication plan, statistical analysis plan (SAP), and list of assessments have been published elsewhere.[27,30–32] Further details on sample, randomization, intervention, assessments, outcomes and covariates are provided in the Supporting Methods.

Sample size and randomization

For its primary cardiovascular disease end point,[30] the SURfit study aimed to recruit 150 participants to detect a 15% difference between study arms (power of 0.80, two-sided α of 0.05, and accounting for a 20% dropout).[27] Minimization randomization performed by an external collaborator ensured unbiased allocation of key prognostic factors; sex and primary cancer diagnosis (leukemia and lymphoma; central nervous system tumors; bone tumors and soft tissue sarcomas; and other diagnoses). For this article, we included participants with valid information on any of the three outcomes at baseline (Figure S1).

Intervention

Participants of the intervention group were asked to increase intense PA/week by ≥2.5 h for 12 months, where 30 minutes were strength

building exercises and two hours aerobic exercises (detailed description in the Supporting Methods). These were based on international recommendations of healthy physical activities (Centers for Disease Control and Prevention: www.cdc.gov). Recommendations were given based on initial physical activity levels, baseline fitness tests, general health status, and participants' preferences and motivation. We used standardized forms for health and medical status, preferences, and barriers with respect to PA, a motivational interview guide, and a guide for the follow-up interview. Study physiotherapists developed personal PA programs in conjunction with participants at baseline and filled a physical activity contract describing the agreed specific activities to implement into their usual week. Participants were additionally given their optimal training heart rate with instruction on how to measure it, as well as a flyer with general tips for aerobic and strength building exercises. The study physiotherapists were trained before study start but also relied on their expertise as exercise specialists to give tailored recommendations. All forms of the intervention and further details of the SURfit study have been previously published.[27,30] Regular contact with physiotherapists at 0, 3, 6, and 12 months and phone calls at 1, 2, 4, 8, and 10 months, a pedometer (model Fitbug Air), and a daily self-managed web-based activity diary served as motivational tools. Participants were reminded weekly of missing diary entries. The activity diary and PA behavior were discussed during clinic visits at 3 and 6 months to discuss compliance, motivation, and progress. Control group participants were given no PA recommendations, which reflect standard follow-up care of CCS in Switzerland. They were offered the same PA program after the 1-year study period.

Assessments

Trained study nurses, sport scientists, or medical physicians assessed participants at the University Children's Hospital Basel, Switzerland at baseline (T0), 3 (T3), 6 (T6), and 12 (T12) months post-randomization using standard operating procedures (SOPs). Assessments comprised clinical examinations, self-reported questionnaires, objective measures of PA, and a cardiopulmonary exercise test (CPET).[27] Activity levels were measured over 2-week periods with ActiGraph GT3X+ accelerometers (100 Hz, 60-s epochs) at T0, T6, and T12. CPETs, as a robust measure of fitness, were conducted using a cycle ergometer. Maximum peak performance was measured as the power (watt [W]) of the last 1-minute stage of the test, plus 5W for each additional 15-s bout of the subsequent unfinished stage.

Psychosocial outcomes

HRQOL

We used the Short Form-36 (SF-36) to measure HRQOL at T0, T6, and T12.[33] We calculated and combined its eight subscales into a physical (PCS) and mental component summary (MCS) score for the effect analyses (further details in the Supporting Methods). Subscales are presented descriptively. T-scores were calculated based on age- and sex-stratified data from a Swiss normative population ($n = 1209$). Higher scores indicate better HRQOL.[34] A dichotomized PCS and MCS were generated for subgroup analyses; a T-score ≤ 40 at baseline meant low PCS or MCS, a score higher than 40 indicated normal HRQOL.[3]

Fatigue

We assessed fatigue during the last 2 weeks at all time points with the validated 20-item Checklist Individual Strength (CIS) questionnaire.[35,36] The subjective fatigue score (CIS8R), a validated score for evaluating experiences of fatigue was used for effect analyses. Inverted items were recalculated so higher sum scores reflect higher degrees of fatigue. We also calculated and descriptively present the remaining three subscales and a global sum score (details in the Supporting Methods). Raw scores were calculated according to the scoring manual and converted to T-scores using a Dutch normative population ($n = 1923$).[37] For subgroup analyses, we dichotomized baseline subjective fatigue scores into "not fatigued" (raw score, 0–26) and "fatigued" (raw score, 27–56).[38]

Psychological distress symptoms

To measure symptoms of psychiatric burden the past 7 days at T0, T6, and T12, we used the Brief Symptom Inventory (BSI-53), a short version of the SCL-90-R.[39–41] Our effect analysis used the Global Severity Index, hereafter "distress symptoms". A higher score indicates greater psychiatric burden. Another nine BSI-53 subscales on distress and two on symptom severity were calculated and presented descriptively. We converted results to T-scores using German sex-stratified normative data ($n = 600$).[39] For subgroup analyses, we classified participants using the scoring manual. A distress symptom score or any two of the nine BSI-53 subscales ≥ 63 at baseline were classified as having "significant distress symptoms", otherwise as "not distressed".[39]

Adverse events

Participants were asked to report adverse events at each time point. These were categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0.[42]

Covariates

We obtained age at study entry, sex, and cancer-related characteristics from medical records. Weight and height were measured at baseline, and calculated body mass index (BMI, kg/m^2). Self-reported

questionnaires were used to assess smoking, education level, work status, and living situation.

Blinding

Group allocation was blinded for some members of the project team (i.e., CPET, blood work, data management, and preparation of the statistical analyses). It was not possible to blind study participants, project physiotherapists, project physicians, and some of the assessors.

Statistical analyses

All statistical analyses were pre-specified in the SAP.[32] We used STATA v.17. A p-value < .05 was considered statistically significant. No adjustments for multiple testing were made because current outcomes were secondary outcomes of a larger trial.

Allocation

Group allocations were based on intention-to-treat (ITT) allocation (primary analysis), assumed compliance, and two variations of reported compliance.[27]

ITT

Intervention and control participants were analyzed as randomized.

Assumed compliance (per-protocol 1 [PP1])

Assumed intervention participants were defined by a ≥5% increase in peak performance (W) from T0–T12 on the CPET, participants were otherwise defined as controls independent of the original randomized groups. This stringent threshold was chosen as an objective measure to clearly distinguish those with improved cardiorespiratory fitness, assuming that such an increase is only seen if PA levels were increased after baseline. Participants without a valid CPET result at both time points were excluded.

Reported compliance (per-protocol 2 [PP2] and per-protocol 3 [PP3])

Only participants compliant to their randomized arm were included. Intervention participants were defined as compliant when reaching two-thirds of their intense PA goal as reported daily in the online diary. Missing days were imputed as (1) zero minutes (PP2), assuming that no data was entered because no activity was performed, or (2) with each participant's annual mean PA (PP3) assuming that the entries were true missing entries even though some activity was performed. Daily reporting increases accuracy and reliability due to reduced recall-bias and long-term PA assessment.[43,44] Control group participants reporting ≤30 min increase in weekly intense PA based on interviews at baseline and T12 were defined as compliant controls.

Descriptives

Baseline socio-demographic and cancer-related characteristics are presented by ITT allocation, with continuous variables reported as means and standard deviations (SDs) and categorical variables as numbers and proportions. Descriptive mean T-scores and raw scores with SDs of main scales and all subscales of HRQOL, fatigue, and distress symptoms are provided by ITT allocation and study time point.

Intervention effect analyses

We assessed intervention effect on psychosocial outcomes with generalized linear mixed models (GLMM) with random intercept, random slope, and treatment-time interaction, adjusting for randomization factors and baseline score. The models included all participants with a valid baseline result of the respective outcome (Figure S1). Our primary analyses were based on ITT allocation, and secondary analyses on PP1, PP2, and PP3 allocation to inform our primary findings. To reduce the number of tests, we emphasize our reporting on ITT outcomes at 12 months, restricted to four outcomes pre-specified in the SAP.[45,46] Effect estimates were change in marginal means with 95% confidence intervals (CI) from baseline to T3 (only available for fatigue), T6, and T12. The post hoc exploratory subgroup analyses were performed by adding an interaction term between ITT group allocation and dichotomized baseline psychosocial outcomes to the GLMM described above.

RESULTS

Participant flow

We invited 842 CCS of whom 151 were randomized (76 intervention, 75 control) (Figure S1). Our modified ITT sample due to missing baseline scores included 74 and 72 in the intervention and controls groups for HRQOL analyses, 74 and 70 for fatigue, and 75 and 73 for distress symptoms. Per-protocol sample sizes are presented in Table 3.

Baseline characteristics and psychosocial outcomes

Mean age at diagnosis was 7.4 years (SD, 4.9) with a mean of 22.0 years (SD, 9.2) since first diagnosis (Table 1). The most common

TABLE 1 Baseline characteristics by study arm.

	Control group N = 75	Intervention group N = 76	Total N = 151
Socio-demographic variables			
Sex, female	33 (44%)	33 (43%)	66 (44%)
Age at study (years)	29.3 (8.7)	31.5 (8.3)	30.4 (8.6)
Smoking	16 (22%)	19 (25%)	35 (23%)
Education, highest completed/current[a]			
Vocational training or less	26 (36%)[b]	25 (33%)	51 (34%)
Upper secondary education	32 (44%)	36 (47%)	68 (46%)
University education/doctorate	14 (19%)	15 (20%)	29 (20%)
Work status[c]			
Full-time/in education/spouse	60 (85%)	63 (83%)	123 (84%)
Part-time	8 (11%)	8 (11%)	16 (11%)
Unemployed/disabled	3 (4%)	5 (7%)	8 (5%)
Living situation			
Single, living alone	10 (14%)	15 (20%)	25 (17%)
Single, living with adults	19 (27%)	17 (23%)	36 (25%)
Single, living with child(ren)[d]	3 (4%)	2 (3%)	5 (3%)
Married/partner, without child(ren)	26 (37%)	25 (34%)	51 (35%)
Married/partner with child(ren)[d]	12 (17%)	15 (20%)	27 (19%)
Clinical variables			
BMI (kg/m^2)	23.7 (4.0)	24.4 (4.3)	24.1 (4.2)
Age at diagnosis (years)	7.3 (4.6)	7.6 (5.1)	7.4 (4.9)
Years since diagnosis	22.0 (9.2)	24.0 (8.6)	23.0 (8.9)
Primary diagnosis (ICCC-3)			
I Leukemia	31 (41%)	24 (32%)	55 (36%)
II Lymphoma	14 (19%)	18 (24%)	32 (21%)
III CNS tumor	6 (8%)	11 (14%)	17 (11%)
IV Neuroblastoma	4 (5%)	2 (3%)	6 (4%)
V Retinoblastoma	4 (5%)	0 (0%)	4 (3%)
VI Renal tumor	5 (7%)	3 (4%)	8 (5%)
VII Hepatic tumor	1 (1%)	0 (0%)	1 (1%)
VIII Bone tumor	3 (4%)	2 (3%)	5 (3%)
IX Soft tissue sarcoma	3 (4%)	8 (11%)	11 (7%)
X Germ cell tumor	1 (1%)	2 (3%)	3 (2%)
XI Other malignant neoplasm	1 (1%)	1 (1%)	2 (1%)
Langerhans cell histiocytosis	2 (3%)	5 (7%)	7 (5%)
Chemotherapy	67 (89%)	69 (91%)	136 (90%)
Anthracyclines	51 (68%)	69 (91%)	120 (79%)
Cumulative anthracycline dose (mg/m^2)	193.9 (97.8)	191.7 (89.3)	192.9 (93.4)
Steroids	45 (60%)	42 (55%)	87 (58%)
Cumulative steroid dose (mg/m^2)	4442.5 (3171.9)	4045.8 (3431.1)	4246.5 (3288.3)

(Continues)

TABLE 1 (Continued)

	Control group *N* = 75	Intervention group *N* = 76	Total *N* = 151
Radiotherapy	30 (40%)	31 (41%)	61 (40%)
Total body irradiation	2 (7%)	3 (10%)	5 (8%)
Cranial irradiation	15 (50%)	12 (39%)	27 (44%)
Abdominal irradiation	7 (23%)	5 (16%)	12 (20%)
Other location	6 (20%)	11 (35%)	17 (28%)
Cranial radiation ≥24 Gy	10 (13%)	10 (13%)	20 (13%)
Stem cell transplantation	4 (5%)	5 (7%)	9 (6%)
Surgery	40 (53%)	46 (61%)	86 (57%)

Note: Continuous outcomes are mean (SD) and categorical variables *n* (%). Number of missing entries by allocation for continuous or categorical variables where not all categories are displayed: "Smoking" [control] = 2; "Cumulative steroid dose" [control] = 3, [intervention] = 1; "Physical activity" [control] = 3, [intervention] = 1.

Abbreviations: BMI, body mass index; CNS, central nervous system; Gy, gray; ICCC-3, International Classification of Childhood Cancer, 3rd ed.

[a]Upper secondary education includes up to bachelor's degrees. University education/doctorate includes postgraduate degrees and higher.

[b]Of which one reported compulsory schooling as highest completed education.

[c]Of those reporting "Working full-time, education, housewife/husbandband," 22 also reported "working part-time" and three reported being "unemployed/disabled." Four among those reporting "working part-time" also reported being "unemployed/disabled."

[d]Child(ren) ≤14 years.

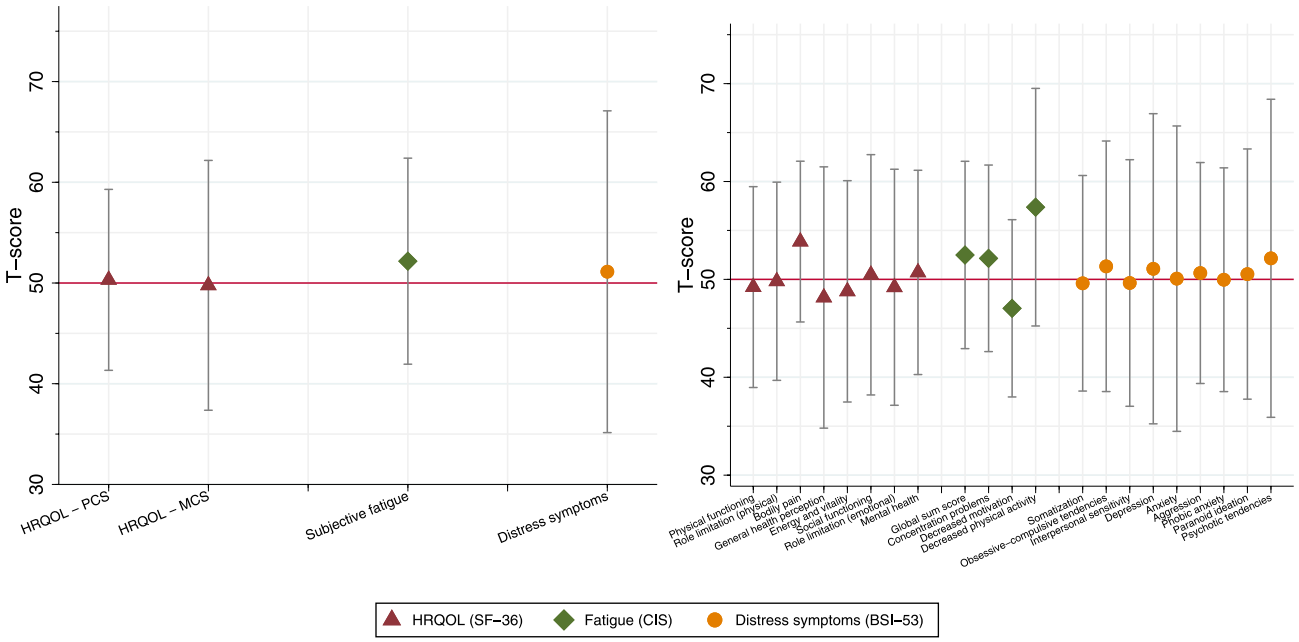

FIGURE 1 Baseline mean T-scores (SD) of primary (left) and subscale (right) psychosocial outcomes. Scores scaled as T-scores (mean = 50, SD = 10) within representative normative populations for each questionnaire. Primary scales on the left side were those used in effect analyses. BSI-53 indicates Brief Symptom Inventory questionnaire; CIS, Checklist Individual Strength questionnaire; HRQOL, health-related quality-of-life; MCS, mental component score; PCS, physical component score; SD, standard deviation; SF-36, Short Form-36 questionnaire.

diagnoses were leukemia (36%), lymphoma (21%), and central nervous system tumors (11%). Baseline characteristics were balanced between randomized groups.

All mean values of psychosocial outcomes were within one SD (40 ≤T-score ≤60) of the normative population means at baseline (Figure 1; Table 2; Table S1). At baseline, 12% and 16% of the intervention group experienced poor physical and mental HRQOL respectively; 11% of controls experienced poor physical HRQOL and 17% poor mental HRQOL. Fatigue was reported by 42% in the intervention group and 35% of controls; 24% of the intervention group and 23% of controls reported being psychologically distressed (Table S2).

TABLE 2 Descriptive mean T-scores and SDs of psychosocial outcomes by ITT allocation and study time point.

	Control			Intervention		
	Baseline	**6 months**	**12 months**	**Baseline**	**6 months**	**12 months**
HRQOL (SF-36)	*n* = 73	*n* = 70	*n* = 70	*n* = 76	*n* = 66	*n* = 60
HRQOL PCS	50.8 (8.7)	51.1 (7.9)	48.9 (10.8)	49.8 (9.3)	50.4 (8.8)	50.5 (15.1)
HRQOL MCS	48.4 (14.5)	50.0 (13.2)	50.9 (12.2)	51.1 (9.9)	50.1 (13.6)	52.0 (13.2)
Physical functioning	49.0 (10.8)	48.7 (10.0)	48.0 (11.8)	49.5 (9.8)	50.5 (6.8)	48.0 (23.8)
Role limitation (physical)	50.2 (9.6)	50.4 (9.2)	47.7 (11.4)	49.5 (10.6)	48.3 (10.5)	48.9 (9.4)
Bodily pain	53.7 (8.4)	53.1 (9.0)	52.9 (10.7)	54.0 (8.0)	53.9 (8.6)	54.9 (7.8)
General health perception	48.3 (12.7)	51.1 (11.1)	49.4 (13.9)	48.0 (14.0)	49.4 (14.2)	52.6 (12.2)
Energy and vitality	48.9 (11.8)	51.0 (9.8)	48.6 (11.5)	48.6 (10.9)	49.2 (12.5)	50.0 (10.9)
Social functioning	49.2 (13.5)	51.2 (11.3)	51.7 (11.0)	51.7 (10.9)	50.0 (13.5)	53.3 (9.1)
Role limitation (emotional)	48.7 (12.4)	48.0 (14.5)	49.5 (11.7)	49.7 (11.8)	49.7 (11.5)	48.6 (11.9)
Mental health	49.0 (11.8)	50.7 (12.0)	51.1 (10.6)	52.4 (8.7)	51.4 (10.3)	53.4 (9.8)
Fatigue (CIS)	*n* = 70	*n* = 67	*n* = 67	*n* = 74	*n* = 64	*n* = 59
Global sum score	52.3 (9.7)	50.2 (10.9)	52.9 (11.1)	52.7 (9.5)	50.5 (10.8)	49.0 (10.8)
Subjective fatigue (CIS8R)	51.8 (10.3)	50.4 (10.8)	53.2 (10.8)	52.5 (10.2)	51.0 (10.8)	50.4 (10.8)
Concentration problems	53.2 (10.0)	51.9 (11.9)	53.0 (11.1)	51.2 (9.0)	51.9 (10.7)	50.1 (10.9)
Decreased motivation	46.8 (9.1)	44.5 (7.0)	47.0 (8.4)	47.3 (9.1)	46.0 (9.6)	45.1 (8.6)
Decreased physical activity	56.4 (12.5)	53.6 (12.3)	55.7 (13.3)	58.3 (11.8)	51.5 (11.8)	49.5 (11.3)
Psychological health (BSI-53)	*n* = 73	*n* = 70	*n* = 70	*n* = 75	*n* = 65	*n* = 61
Distress symptoms (GSI)	52.6 (18.3)	50.5 (15.3)	50.0 (15.5)	49.7 (13.3)	49.6 (16.0)	50.3 (17.6)
PSDI	52.4 (12.5)	53.0 (16.6)	51.4 (11.2)	50.0 (9.3)	49.7 (11.4)	50.8 (11.7)
Positive symptom total	50.6 (11.8)	49.0 (12.8)	48.7 (12.5)	48.9 (12.2)	48.0 (12.5)	48.6 (14.0)
Somatization	49.3 (10.3)	50.2 (11.4)	50.2 (14.6)	49.9 (11.7)	49.7 (12.7)	50.3 (12.5)
Obsession–compulsion	53.0 (14.6)	51.0 (11.3)	51.4 (13.4)	49.7 (10.6)	49.4 (11.8)	51.1 (13.3)
Interpersonal sensitivity	50.2 (13.5)	48.4 (13.6)	47.9 (9.3)	49.0 (11.7)	48.5 (12.6)	48.3 (12.8)
Depression	52.4 (19.0)	51.1 (16.3)	49.7 (13.8)	49.8 (12.0)	49.6 (14.8)	49.6 (14.1)
Anxiety	51.1 (19.4)	48.5 (14.3)	46.9 (9.3)	49.1 (10.8)	47.7 (10.8)	49.5 (12.9)
Aggression	52.8 (12.1)	50.4 (11.5)	49.9 (10.1)	48.6 (10.1)	52.5 (13.8)	49.4 (10.8)
Phobic anxiety	49.7 (10.2)	49.7 (12.8)	51.4 (18.1)	50.2 (12.6)	49.3 (11.2)	49.8 (16.0)
Paranoid ideation	51.4 (12.7)	51.2 (14.2)	50.2 (12.3)	49.7 (12.9)	49.2 (14.3)	49.6 (15.1)
Psychotic tendencies	54.3 (19.0)	51.3 (13.5)	50.6 (12.7)	50.1 (12.8)	51.0 (17.8)	52.3 (21.6)

Note: Effect analyses used HRQOL PCS and MCS, subjective fatigue (CIS8R), and distress symptoms (GSI) scales, highlighted in italic.

Abbreviations: BSI-53, Brief Symptom Inventory questionnaire; CIS, Checklist Individual Strength questionnaire; GSI, global severity index; HRQOL, health-related quality-of-life; ITT, intention-to-treat; MCS, mental component score; PCS, physical component score; PSDI, positive symptom distress index; SF-36, Short Form-36 questionnaire.

Compliance

A total of 19 (13 intervention and 6 control group) participants dropped out throughout the study period, mainly because they were lost-to follow-up or the study was too time-consuming (Figure S1).

Among 112 participants with valid CPET measurements at baseline and T12, 36 (24% of 151) increased their peak performance by ≥5% and were considered assumed intervention, 76 (50%) were assumed controls (PP1). There were 19 (13%) dropouts and 20 (13%) who did not have valid CPET data. With missing diary entries set to zero (PP2), 35 (46% of 76 originally allocated) of the intervention group reached two-thirds or more of their PA goals, and 40 (53%) when missing days were set to their annual mean (PP3). In both PP2 and PP3, of 75 allocated controls, 47 participants (63%) were

compliant and 19 (25%) were dropouts. Details on compliance have been previously published.[47]

Adverse events

A total of 170 adverse events (AEs) were registered, 91 in the intervention and 78 in the control group.[30] Eleven events were likely related to the intervention. Two were linked to back pain, two were psychosocial adverse events, and two were other types of injuries. The remaining five events were due to strain or overstretching, with four occurring in the ankle ligaments (Table S3). Of overall four serious AEs, one was severe psychiatric disorder in the intervention group. Psychosocial AEs otherwise included depression (reported six times in the intervention group and once by a control) and psychiatric disorders (one report in the intervention group that also resulted in withdrawal from the study). In total, three participants in the intervention group withdrew from the study due to AEs, none in the control group.

Effect of PA intervention on psychosocial outcomes

Descriptive changes in the intervention group showed increased PCS and MCS scores and decreased fatigue and distress symptoms scores at T12 compared to baseline (Table 2; Table S1; Figure S2). The control group reported increased mean MCS and fatigue scores and decreased PCS and distress symptoms scores.

Our ITT analyses found significantly larger decrease in fatigue from baseline to T12 in the intervention group compared to controls with a marginal mean difference of −3.56 (95% CI, −5.69 to −1.43, $p = .001$). No other significant differences were found for either physical (ΔT-score: 2.15; 95% CI, −0.22 to 4.52, $p = .075$) or mental (ΔT-score: −1.30; 95% CI, −3.95 to 1.36, $p = .339$) component HRQOL, nor distress symptoms (ΔT-score: 1.57; 95% CI, −1.18 to 4.32, $p = .262$) (Table 3; Figure 2).

Per-protocol analyses (Table 3; Figure 2) had comparable results. Fatigue improved significantly more in both PP2 and PP3 analyses comparing intervention to control group. PCS improved significantly more from baseline to T12 in PP1 (ΔT-score: 3.06; 95% CI, 0.99–5.14, $p = .004$) and PP2 (ΔT-score: 3.54; 95% CI, 1.13–5.96, $p = .004$) analyses. No effect of the intervention was found on mental component HRQOL or distress symptoms across all per-protocol analyses.

Percentage fatigued decreased from 42% to 37% in the intervention group and increased from 35% to 40% in controls (Table S2). Proportion with poor PCS remained the same in the intervention group at 12% from baseline to T12 but increased from 11% to 19% in controls. For MCS the proportion decreased in both intervention group participants (16% to 12%) and controls (17% to 13%). Participants psychologically distressed went from 24% to 18% in the intervention group and 23% to 21% in controls.

Post hoc subgroup analyses

We found no evidence for effect modification by subgroups (all $p_{interaction} > .05$) (Figure 3; Table S4). We found significantly larger reductions in fatigue among the intervention group compared to controls in both the nonfatigued and fatigued subgroup at T12 by −3.40 (95% CI, −6.08 to −0.71, $p = .013$) and −3.38 (95% CI, −6.73 to −0.04, $p = .047$) (Table S4).

DISCUSSION

Our personalized PA intervention significantly reduced fatigue after 12 months among adult long-term survivors of childhood cancer. Furthermore, those compliant to the intervention experienced improved physical HRQOL. Even small effects could have considerable long-term benefits as psychosocial late-effects are results of accumulated risk over a lifetime.

Comparison with previously published RCTs suggests that to achieve sustained effects on fatigue, a longer PA intervention of at least half a year could be necessary. In contrast to the 12-week Fit-Survivor study,[22] Li et al.[19] found reduced levels of fatigue in their 6-month PA intervention after 12 months among fatigued CCS. Our intervention already had an effect after 3 months, which became even stronger after 1 year. HRQOL, as well as actual increased PA levels, seems likewise dependent on a longer intervention period. Three related 6-month adventure-based RCTs found improved HRQOL 12-months post-intervention,[18,19,23,24] whereas the remaining four RCTs on HRQOL found no effects 3 months post-intervention.[17,20–22]

To our knowledge, Fit4Life is the only RCT that has investigated the effect of PA on mental health, yet as a secondary outcome and in CCS of acute lymphoblastic leukemia only.[25] The authors found decreased negative mood as a result of their 4-month web-phone SMS-based weight management intervention, but no significant effect on the four other subscales of the Children's Depression Inventory (CDI).

Our findings support existing guidelines for PA interventions that reduce fatigue and improve physical HRQOL in cancer survivors.[48] The guidelines are, however, complicated by heterogenous exercise modes and supervision, often not tailored to CCS, lacking intensity information, with an overrepresentation of major cancer types such as breast and prostate cancer. The SURfit study contributes to the evidence base of benefits of intense PA for all long-term CCS. We moreover recommend including exercises to stretch and strengthen ankle ligaments and muscles in survivors with reduced range of motion, as four of 11 reported adverse events were related to strain/overstretching of these. Limited range of dorsiflexion in the ankle is a known late effect in CCS that could increase risk for such traumas.[49] Other study designs, such as stepped wedge or single-case experimental designs, as well as other methods such as mediation analysis could further shed light on motivations and mechanisms of PA interventions on psychosocial health. A mediation analysis could for example explore whether the

TABLE 3 Intervention effect with change from baseline in marginal mean T-scores (95% CI) by group allocation for ITT and three per-protocol analyses.

	Months	Control	Intervention	Difference	*p*
ITT					
HRQOL PCS	6	0.12	0.80	0.68	.565
(C: 72; I: 74)		(−1.49 to 1.73)	(−0.87 to 2.47)	(−1.64 to 3.00)	
	12	−1.83	0.32	2.15	.075
		(−3.44 to −0.22)	(−1.42 to 2.06)	(−0.22 to 4.52)	
HRQOL MCS	6	0.59	−1.33	−1.92	.149
(C: 72; I: 74)		(−1.21 to 2.40)	(−3.20 to 0.55)	(−4.52 to 0.69)	
	12	1.05	−0.25	−1.30	.339
		(−0.76 to 2.85)	(−2.19 to 1.70)	(−3.95 to 1.36)	
Fatigue	3	0.60	−2.76	−3.36	.002
(C: 70; I: 74)		(−0.85 to 2.04)	(−4.26 to −1.27)	(−5.44 to 1.28)	
	6	−1.06	−1.84	−0.78	.467
		(−2.52 to 0.41)	(−3.33 to −0.34)	(−2.87 to 1.32)	
	12	1.47	−2.10	−3.56	.001
		(0.00–2.93)	(−3.64 to −0.55)	(−5.69 to 1.43)	
Distress symptoms	6	−0.50	−0.49	0.00	.999
(C: 73; I: 75)		(−2.37 to 1.38)	(−2.44 to 1.46)	(−2.70 to 2.71)	
	12	−0.56	1.01	1.57	.262
		(−2.43 to 1.31)	(−0.99 to 3.02)	(−1.18 to 4.32)	
PP1					
HRQOL PCS	6	0.21	2.18	1.97	.061
(C: 92; I: 35)		(−0.92 to 1.35)	(0.47–3.89)	(−0.09 to 4.02)	
	12	−0.64	2.42	3.06	.004
		(−1.82 to 0.53)	(0.71 to 4.13)	(0.99 to 5.14)	
HRQOL MCS	6	−0.87	−0.94	−0.06	.964
(C: 92; I: 35)		(−2.35 to 0.60)	(−3.16 to 1.29)	(−2.74 to 2.61)	
	12	−0.11	−0.90	−0.79	.568
		(−1.63 to 1.41)	(−3.12 to 1.33)	(−3.49 to 1.92)	
Fatigue	3	−0.55	−2.40	−1.86	.146
(C: 91; I: 35)		(−1.92 to 0.82)	(−4.50 to −0.31)	(−4.36 to 0.65)	
	6	−0.89	−2.67	−1.78	.164
		(−2.28 to 0.50)	(−4.76 to −0.58)	(−4.30 to 0.73)	
	12	0.27	−1.61	−1.87	.148
		(−1.17 to 1.70)	(−3.70 to 0.48)	(−4.41 to 0.67)	
Distress symptoms	6	−0.38	−0.70	−0.32	.839
(C: 93; I: 35)		(−2.07 to 1.31)	(−3.27 to 1.87)	(−3.40 to 2.76)	
	12	0.28	−0.23	−0.51	.747
		(−1.45 to 2.01)	(−2.80 to 2.34)	(−3.62 to 2.59)	
PP2					
HRQOL PCS	6	−0.41	0.86	1.27	.302
(C: 45; I: 54)		(−2.20 to 1.38)	(−0.75 to 2.47)	(−1.14 to 3.68)	

(Continues)

TABLE 3 (Continued)

	Months	Control	Intervention	Difference	*p*
	12	−2.27	1.27	3.54	.004
		(−4.04 to −0.51)	(−0.38 to 2.91)	(1.13–5.96)	
HRQOL MCS	6	1.61	−0.91	−2.52	.111
(C: 45; I: 54)		(−0.68 to 3.91)	(−2.98 to 1.16)	(−5.63 to 0.58)	
	12	1.09	0.01	−1.07	.499
		(−1.18 to 3.35)	(−2.09 to 2.12)	(−4.18 to 2.04)	
Fatigue	3	0.39	−3.42	−3.82	.002
(C: 44; I: 54)		(−1.43 to 2.22)	(−5.08 to −1.76)	(−6.29 to −1.34)	
	6	−1.11	−2.21	−1.11	.381
		(−2.95 to 0.74)	(−3.86 to −0.57)	(−3.58 to 1.37)	
	12	1.81	−2.44	−4.25	.001
		(−0.02 to 3.63)	(−4.11 to −0.77)	(−6.73 to −1.77)	
Distress symptoms	6	−1.46	−0.81	0.65	.655
(C: 46; I: 55)		(−3.57 to 0.64)	(−2.73 to 1.11)	(−2.21 to 3.51)	
	12	−0.66	−0.28	0.38	.795
		(−2.75 to 1.42)	(−2.22 to 1.66)	(−2.48 to 3.24)	
PP3					
HRQOL PCS	6	−0.36	1.23	1.59	.274
(C: 45; I: 59)		(−2.51 to 1.79)	(−0.63 to 3.09)	(−1.26 to 4.43)	
	12	−2.23	0.38	2.61	.072
		(−4.35 to −0.10)	(−1.51 to 2.27)	(−0.24 to 5.46)	
HRQOL MCS		1.73	−1.44	−3.17	.052
(C: 45; I: 59)		(−0.68 to 4.13)	(−3.52 to 0.63)	(−6.36 to 0.02)	
	12	1.19	−0.14	−1.33	.414
		(−1.19 to 3.57)	(−2.25 to 1.97)	(−4.53 to 1.86)	
Fatigue	3	0.31	−3.16	−3.47	.006
(C: 44; I: 59)		(−1.57 to 2.19)	(−4.80 to −1.51)	(−5.97 to −0.97)	
	6	−1.19	−2.25	−1.06	.405
		(−3.09 to 0.70)	(−3.87 to −0.63)	(−3.56 to 1.44)	
	12	1.73	−2.31	−4.03	.002
		(−0.15 to 3.60)	(−3.95 to −0.67)	(−6.53 to −1.54)	
Distress symptoms	6	−1.58	−0.34	1.25	.465
(C: 46; I: 60)		(−4.10 to 0.93)	(−2.53 to 1.86)	(−2.09 to 4.59)	
	12	−0.78	1.03	1.81	.289
		(−3.26 to 1.71)	(−1.18 to 3.24)	(−1.53 to 5.14)	

Note: GLMM with random intercept, random slope, and treatment-time interaction, adjusting for sex, main cancer diagnosis group, and baseline scores. Group allocation differed for ITT, PP1, PP2, and PP3 analyses. Scores are change in marginal mean T-scores from baseline to 3- (if available), 6-, and 12-months post-randomization. Includes all participants with valid baseline measurements of the respective outcome; sample size in each model is indicated as C (control group): number; and I (intervention group): number.

Abbreviations: C, control sample size; CI, confidence interval; GLMM, generalized linear mixed model; HRQOL, health-related quality-of-life; I, intervention sample size; ITT, intention-to-treat; MCS, mental component summary score; PCS, physical component summary score; PP1, per-protocol 1 model (allocation based off assumed compliance through exercise tests); PP2, per-protocol 2 model (allocation based off reported compliance through web-diaries, missings set as 0); PP3, per-protocol 3 model (allocation based off reported compliance through web-diaries, missings set as yearly mean).

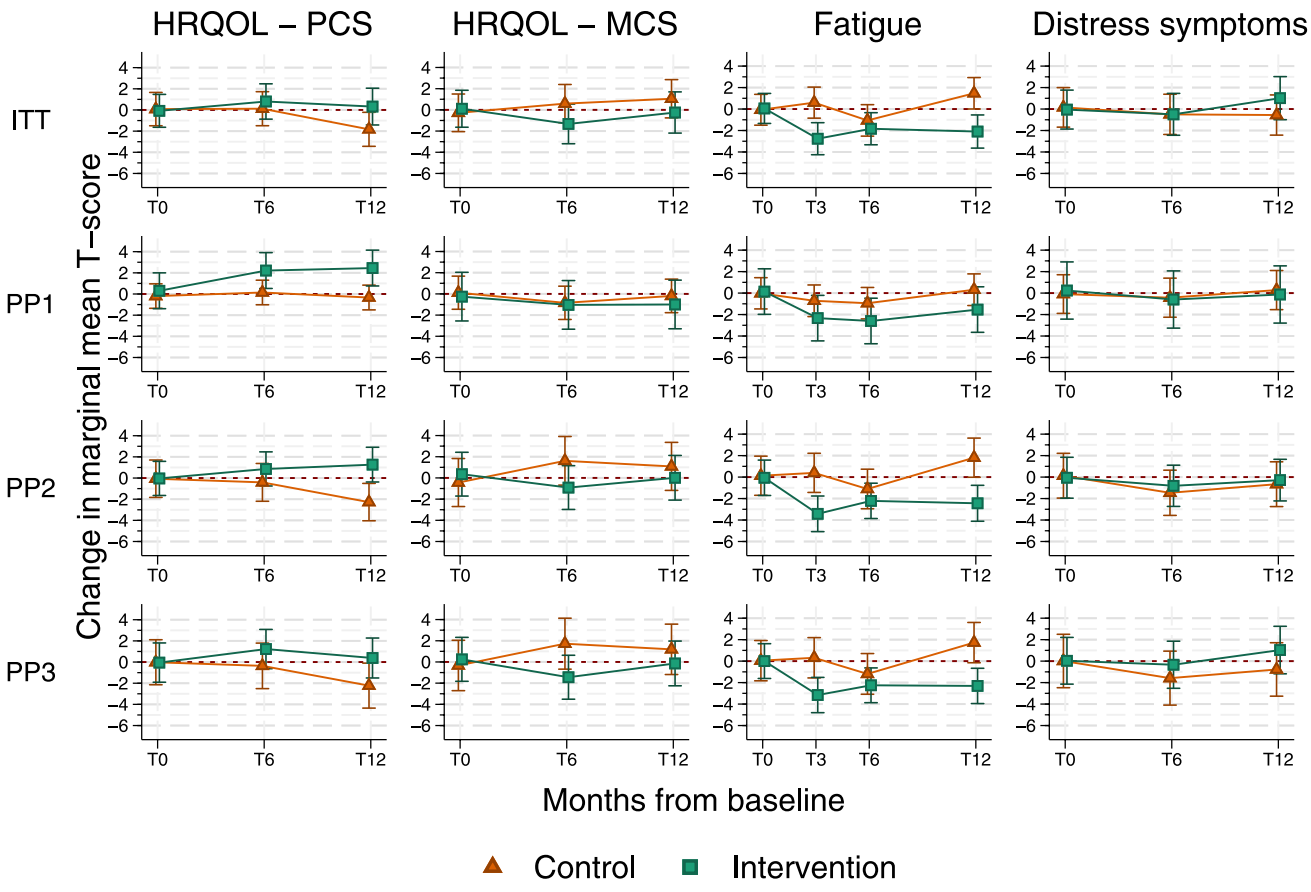

FIGURE 2 Intervention effect with change from baseline in marginal mean T-scores (95% CI) by group allocation, for ITT and three per-protocol analyses. GLMM with random intercept, random slope, and treatment–time interaction, adjusting for sex, main cancer diagnosis group, and baseline scores. Group allocation differed for ITT, PP1, PP2, and PP3 analyses. Scores are change in marginal mean T-scores from baseline to 3- (if available), 6-, and 12-months post-randomization. Includes all participants with valid baseline measurements of the respective outcome. See Table 3 for exact estimates and number of participants in each model. CI indicates confidence interval; GLMM, generalized linear mixed model; HRQOL, health-related quality-of-life; ITT, intention-to-treat model; MCS, mental component score; PCS, physical component score; PP1, per-protocol 1 model (allocation based off assumed compliance through exercise tests); PP2, per-protocol 2 model (allocation based off reported compliance through web-diaries, missings set as 0); PP3, per-protocol 3 model (allocation based off reported compliance through web-diaries, missings set as yearly mean).

decrease in fatigue can be explained by an increase in physical fitness. Although only around a fifth of the intervention group reached our strict compliance threshold, our intervention was overall effective in increasing cardiorespiratory fitness.[30]

Targeting the entire population of CCS and not only those already fatigued seems a reasonable necessity. The SURfit study addresses an important knowledge gap for long-term CCS with a special emphasis on adult CCS in which average years since diagnosis was 22.0 years (SD, 9.2). PA interventions could mitigate the negative trend of fatigued survivors as up to 62% of adult CCS experience fatigue versus just 13% of child CCS.[6] In support of the literature, we also saw an increase in proportion fatigued among our controls after a year (from 35% to 40%). In those not fatigued at baseline, our intervention seemed to maintain baseline fatigue scores whereas controls worsened. Moreover, although no longitudinal studies have investigated fatigue from treatment to late remission (≥5 years post-treatment), one small cross-sectional study found fatigue was highest for those in treatment, lowest 1–2 years after treatment, but higher again in late remission, suggesting that the timing of our intervention was well suited to reach a population at increasing risk of fatigue.[50]

Minimal clinically important differences (MCIDs) help in evaluating whether statistically significant findings are clinically relevant. Although there are no validated MCIDs for the CIS fatigue score, both 0.25 and 0.50 SDs can generally be used for patient-reported outcome measures, correspondingly a T-score of 2.5 and 5.0.[51,52] Our mean difference of change in the fatigue score of −3.56 in favor of the intervention group lies between these. In addition, individual fatigue trajectories revealed variations in change of fatigue over time, suggesting that some individuals benefit to an even larger extent (Figure S2). Of special note is that a recent review issued a strong recommendation for using PA interventions to manage fatigue in children and adolescents on and off cancer therapy, reporting a standardized mean difference of 0.44 (similar to a T-score of 4.40) across 18 included RCTs.[53] We therefore consider our results promising because we reached a similar change in a population long after cancer treatment and at risk of persistent and increasing levels of fatigue.[6]

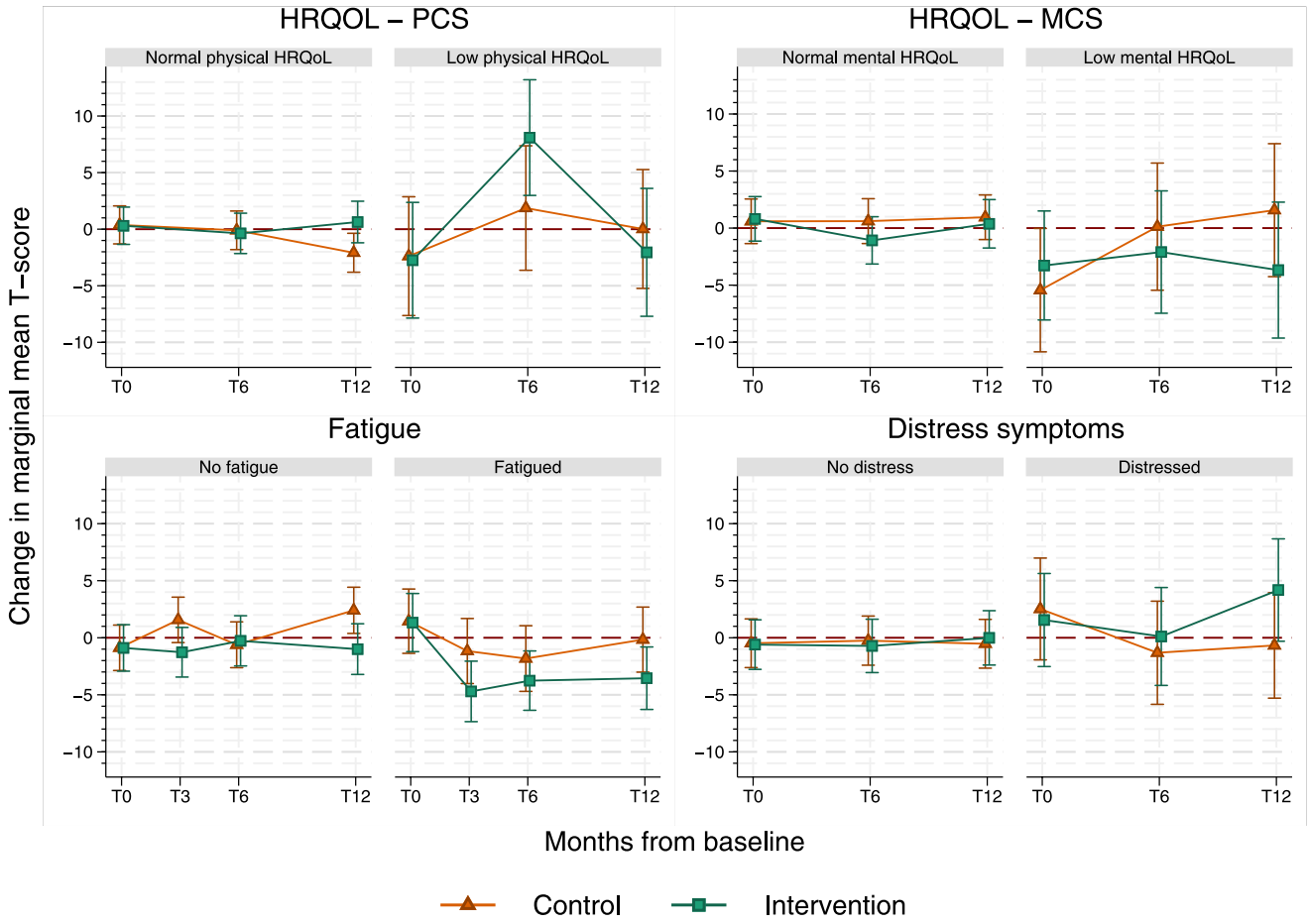

FIGURE 3 Post hoc subgroup analyses of change from baseline in marginal T-scores (95% CI) by ITT allocation and normal versus poor psychosocial health. Generalized linear mixed model (GLMM) with random intercept, random slope, and time-treatment-subgroup interaction, adjusting for sex, main cancer diagnosis group, and baseline scores. Allocation according to ITT. Scores are change in marginal mean T-scores from baseline to 3- (if available), 6-, and 12-months post-randomization. Includes all participants with valid baseline measurements of the respective outcome. See Table S4 for exact estimates. *p* values for interaction effect between allocation and subgroups from baseline to 12 months were: HRQOL PCS: $p_{interaction}$ = .348; HRQOL MCS: $p_{interaction}$ = .162; fatigue: $p_{interaction}$ = .960; distress symptoms: $p_{interaction}$ = .185. CI indicates confidence interval; GLMM, generalized linear mixed mode; HRQOL, health-related quality-of-life; ITT, intention-to-treat model; MCS, mental component score; PCS, physical component score.

Interventions that alter this trend for the better should warrant deliberate attention. Furthermore, 5% more survivors of the control group were above the fatigue cutoff after 1 year, compared to 5% less survivors of the intervention group were fatigued after 1 year.

A strength of the SURfit study as a high-quality RCT is its strict adherence to guidelines for confirmatory trials, detailed SOPs for assessments, and a pre-specified SAP. It is novel in including a personalized intervention of 1 year, multiple motivational tools, and regular follow-ups over 1 year, especially in comparison with previous RCTs that only intervened for 6 months or less. We also had few dropouts enabling us to detect long-term changes in important patient-related outcomes. A limitation was the possibility of ceiling effects, which could reduce sensitivity in detecting larger intervention effects. Conversely, other studies that only focus on individuals already low on psychosocial health and high in fatigue could more easily identify larger intervention effects.[54,55] Similar effect sizes were however found in both fatigued and nonfatigued participants in our post hoc analyses. Furthermore, only 18% of invited survivors were randomized, however, no differences in important baseline characteristics were found between nonparticipants based on data from the Swiss Childhood Cancer Registry and our study sample, suggesting a representative sample of adult CCS.[56] Moreover, although we excluded some participants due to missing baseline values (three to seven participants), we believe that these can be considered missing at random and would not have a significant impact on our overall results. Another limitation is our study's comprehensive and resource demanding intervention. Graded implementation into clinical practice should be considered to find optimal cost-to-effect ratios.

In conclusion, the SURfit study showed that our PA intervention over 12 months improved fatigue in adult CCS regardless of initial fatigue levels. CCS are a growing population at substantial risk for psychosocial sequelae that should be targeted by clinicians. PA should be recommended to all survivors in follow-up care as a cheap and safe preventive measure, especially to those with symptoms of

fatigue, thereby informing the evidence-based practice in follow-up care of CCS.

AUTHOR CONTRIBUTIONS

Wei H. Deng: Data curation, formal analysis, methodology, validation, visualization, writing–original draft, and writing–review and editing. **Simeon J. Zürcher**: Investigation, writing–review and editing, methodology, project administration, validation, and visualization. **Christina Schindera**: Investigation, writing–review and editing, funding acquisition, methodology, project administration, resources, validation, and visualization. **Ruedi Jung**: Data curation, investigation, writing–review and editing, project administration, and validation. **Helge Hebestreit**: Conceptualization, writing–review and editing, methodology, and validation. **Iris Bänteli**: Investigation, writing–review and editing, data curation, and project administration. **Katja Bologna**: Writing–review and editing, and investigation. **Nicolas X. von der Weid**: Conceptualization, funding acquisition, investigation, writing–review and editing, project administration, resources, visualization, validation, and software. **Susi Kriemler**: Conceptualization, funding acquisition, project administration, writing–review and editing, resources, validation, visualization, software, and methodology. **Corina S. Rueegg**: Conceptualization, investigation, methodology, writing–review and editing, project administration, data curation, resources, supervision, visualization, funding acquisition, writing–original draft, validation, software, and formal analysis.

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We thank all participants for taking part in our study. We thank the study nurses, assistants, master students, and physiotherapists for their great work within the study. The study was performed in accordance with the Declaration of Helsinki and approved by the Swiss Ethics Committee on research involving humans (Ethikkommision Nordwest-und Zentralschweiz [EKNZ], EKNZ-2015-169). Informed consent as documented by signature was obtained from each survivor before participation in the study. Data protection is assured by pseudonymization and secure storage of sensitive data.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

De-identified individual participant data that underlie the results reported in this article, statistical programs, and data dictionary are available on request to the corresponding author, immediately following publication and without end date, to anyone who provides a sound proposal. The study protocol, statistical analysis plan, patient information and informed consent forms are published at the Open Science Framework platform (https://osf.io/w6j4y/).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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