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Effect of a Physical Activity Intervention on Lower Body Bone Health in Childhood Cancer Survivors: A Randomised Controlled Trial (SURfit)

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Abbreviations:

BMD	Bone mineral density (mg/cm^3 or g/cm^2)
CCS	Childhood cancer survivor(s)
CPET	Cardiopulmonary exercise test
DXA	Dual-energy X-ray absorptiometry
ITT	Intention-to-treat analysis
PA	Physical activity
pQCT	Peripheral quantitative computed tomography
RCT	Randomized controlled trial

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What's new?

It is still controversial whether physical activity promotes bone health in childhood cancer survivors (CCS). This is one of the first RCT with a relatively large population of CCS investigating lower body bone health in an individualized one-year exercise program. There were no statistically and clinically significant difference between the intervention and control group for any bone parameters, although those compliant and those with initial osteopenia may indeed improve bone health.

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Abstract

It is still controversial whether physical activity promotes bone health in childhood cancer survivors (CCS). We aimed to assess the effect of a one-year general exercise intervention on lower body bone parameters of CCS. CCS ≥16y at enrollment, <16y at diagnosis, and ≥5y in remission were identified from the national Childhood Cancer Registry. Participants randomized to the intervention group were asked to perform an additional ≥2.5h of intense physical activity/week, controls continued exercise as usual. Bone health was assessed as a secondary trial endpoint at baseline and after 12-months. We measured tibia bone mineral density (BMD) and morphology by peripheral quantitative computed tomography and lumbar spine, hip, and femoral neck BMD by dual-energy X-ray absorptiometry. We performed intention-to-treat, per protocol, and an explorative subgroup analyses looking at low BMD using multiple linear regressions. 151 survivors (44% females, 7.5±4.9y at diagnosis, 30.4±8.6y at baseline) were included. Intention-to-treat analysis revealed no differences in changes between the intervention and control group. Per protocol analyses showed evidence for an improvement in femoral neck and trabecular BMD between 1.5-1.8% more in participants being compliant with the exercise program. Trabecular BMD increased 2.8% more in survivors of the intervention group with BMD z-score ≤-1 compared to those starting at z-score >-1. A non-standardized personalized exercise programs might not be specific enough to promote bone health in CCS, although those compliant and those most in need may benefit. Future trials should include bone stimulating exercise programs targeting risk groups with reduced bone health and motivational features to maximize compliance.

INTRODUCTION

Childhood cancer survivors (CCS) have an increased risk for late complications including decreased bone mineral density (BMD) and related fractures.[1,2] Up to 65% of CCS show low BMD dependent on treatment and cancer history. This is partly explained by an impairment in peak bone mass acquisition due to direct or indirect (e.g. growth hormone deficiency, and hypogonadism) effects of chemotherapy and radiotherapy as well as the cancer itself.[1-3] Furthermore, childhood cancer patients during and after cancer treatment frequently experience side effects such as fatigue, nausea, pain, and depression that negatively influence bone acquisition through lack of physical activity (PA) or nutritional deficits.[1,2,4] Moreover, reduced PA levels often persist after cancer therapy.[2,4-6] Although evidence is scarce, international follow-up guidelines for childhood cancer survivors recommend regular weight-bearing exercises such as running and jumping as part of aftercare even during adulthood to maintain or improve bone health.[7]

A physically active lifestyle has in general been associated with improved overall health, lowered risk of developing cancer, and increased bone health.[8,9] Evidence shows that adult cancer patients benefit from regular exercise for multiple cancer-related adverse effects; including physical functioning, fatigue, sexual function, psychological well-being, and quality of life.[10,11] Yet, the body of knowledge on benefits of exercise on bone health among CCS is still sparse and controversial.[2,12] Some small or exploratory observational studies found a positive association between PA and BMD among young CCS.[13-17] A one-year randomized controlled trial (RCT) observed that low-magnitude mechanical stimulation improved whole-body BMD among young CCS while tibial trabecular BMD improved among those with highest intervention-adherence.[18] Another study, however, found no effect on BMD following a two-year exercise program among children with leukemia.[19] There is thus a striking lack of intervention studies that investigate exercise benefits on bone health in CCS.

In this study, we performed a RCT that included a one year individualized, partially supervised general exercise program in a sample of adolescent and adult CCS.[20] We looked at the effects of regular general exercise training on lower body densitometric and architectural bone outcomes measured by dual-energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT), defined as secondary endpoints of the SURfit trial. We hypothesized that our exercise program would benefit lower body bone health.

METHODS

Study design and participants

Data for this publication were drawn from the SURfit study (ClinicalTrials.gov identifier: NCT02730767).[20] SURfit was a single-center, two-armed (parallel) superiority RCT with a one-year PA intervention for adolescent and adult CCS. It was conducted at the University Children's Hospital Basel, Switzerland, between September 2015 and February 2019. The objectives of SURfit were to assess the effects of a one year exercise program on cardiovascular health (primary outcome), and among others on bone health (secondary outcome) in CCS. We included CCS diagnosed with cancer based on the International Classification of Childhood Cancer, third edition[21], or Langerhans cell histiocytosis treated at a Swiss Pediatric Oncology Group clinic, aged ≥16y at enrollment, <16y at diagnosis, and ≥5y since the last cancer event.

Procedures

Eligible CCS were identified from the national, population-based Childhood Cancer Registry[22] and contacted by letter between June 2015 and February 2018 (see **Fig 1**). Eligible CCS who consented to participate were randomly allocated 1:1 with (web-based) minimization randomization by a person independent of the study. Stratification factors for the minimization were gender and four cancer categories (leukemia/lymphoma, central nervous system tumors, bone tumors/soft tissue sarcomas, or other tumor diagnoses). Assessments were performed at baseline (T0) and after 12 months (T12). Blinding of assessors was assured for DXA and the statistical analyses.

Bone outcomes

Bone health was measured by pQCT (XCT 2000; Stratec Medical, Pforzheim, Germany) and DXA (Discovery A densitometer; Hologic, Bedford, MA, USA). Quality assurance of both devices was checked and if needed calibrated before each measuring day according to manufacturers' guidelines. Volumetric BMD, bone mass, and bone geometry were measured using pQCT at the distal epiphysis (4%) and diaphysis (66%) of the tibia in the non-dominant lower leg.[20] Bone outcome parameters were

defined a priori by experts and were total and trabecular volumetric BMD at 4% of tibia length, cortical volumetric BMD, total cortical cross-sectional area, and strength-strain index at 66% tibia length. Outcomes by DXA included femoral neck, total hip, and lumbar spine areal BMD by age and gender matched z-scores.[23] **Supplemental Appendix 1** provides the rationale for some changes in the bone outcome parameters from the ones pre-registered in the clinical trials registry.

Covariates

Demographic and medical information was extracted from medical records or measured at baseline.[20] Lean body and fat mass were measured by DXA and muscular cross-sectional area at tibia 66% by pQCT. PA at baseline was assessed by ActiGraph® GT3X+ (Pensacola, Florida, USA) accelerometer (100Hz, 60s epochs). Daily minutes spent in moderate-to-vigorous PA averaged across all valid days (≥10h wear-time between 6am and 10pm) were calculated using ActiLife v6.13.4.[24] Cardiopulmonary exercise testing (CPET) on a stationary bike was used to estimate change in maximum peak performance in Watts between baseline and post-intervention.[20] Smoking status, vitamin D supplementation, and calcium supplementation were assessed through self-reported standardized questionnaires.

Intervention and control conditions

The intervention group was asked to add ≥2.5h of intense PA/week. Intense PA programs were developed with a professional coach (physiotherapist) and comprised 2h aerobic and 0.5h of strength building exercises. Regular contact with the coach (face-to-face at 0, 3, 6 and 12 months, and phone calls after 1, 2, 4, 5, 8 and 10 months), pedometers, and a self-administered web-based daily activity diary for the one year study duration were used as motivational tools. Participants were reminded weekly of missing diary entries. The control group was asked to keep their activity levels constant.[20] Compliance to the intervention/control group was defined as: **a) reported compliance** includes only participants of the intervention group who reached ≥2/3 of the intense PA goal (web-based diary, missing values were either set to 0 min daily PA or imputed with participant's yearly PA mean) and

controls who reported ≤30 min increase in intense weekly PA (questionnaire); and, **b) assumed compliance** allocates participants to the intervention group if they improved peak work rate by ≥5% from T0 to T12 by CPET irrespective of their randomized treatment allocation. Participants with less increase in work rate were handled as controls. Only the following exercise tests were taken into consideration: either maximal or sub-maximal (sub-maximal at same level) effort at both time points, or improvement of performance despite less effort at T12.

Statistical analyses

Required sample size for SURfit was estimated based on the primary trial endpoint (cardiovascular disease risk score) and resulted in 60 participants in each arm.[20] We aimed at 150 participants to account for a 20% dropout rate. All statistical analyses were pre-defined (before unblinding of the data) and detailed in the statistical analysis plan. Group differences in bone parameters were estimated using analyses of covariance (ANCOVA) adjusted for age, minimization randomization factors (sex and tumor type), and baseline bone outcomes. Beta coefficients (Beta) with 95% confidence intervals (95%CI) are shown for all models. Relative changes of Beta were calculated based on baseline parameters. A p-value ≤0.05 was considered statistically significant. For graphical illustration, z-standardized beta coefficients were used.[23] The following pre-specified analyses were performed according to the study protocol:[20] **Intention-to-treat (ITT)** with last observation carried forward (LOCF) as primary analysis was conducted. Further pre-specified analyses included complete case analysis, per protocol analyses (PP) based on reported (online diary entries) and assumed (Watt performance on stationary bike) compliance, and a dose response assessment as described in **Supplemental Appendix 2**. **Exploratory subgroup analyses** were performed for bone parameters of intervention participants showing low BMD (z-score ≤-1) at baseline[25] by adding an interaction term between group allocation and low baseline BMD in those without missing outcome measures. R v4.0.2[26] was used for regression data analyses and graphical plotting.

RESULTS

Study sample

From 1450 eligible CCS, 842 were invited and received basic study information. A total of 151 CCS (18%) were eligible and randomly assigned to one of the two treatment arms of which 132 (87%) completed the entire study; 13 participants from the intervention group and 6 controls (together 13%) dropped out for various reasons (**Fig 1**).

Mean age at baseline of the 151 participants was 30.4±8.6 years (range 17-49 years); 66 (44%) were female (**Table 1**). Tumor type, treatment, bone parameters and PA were well matched between groups.

Analysis sets and intervention adherence

All 75 control and 76 intervention group participants were considered in the ITT and complete case analysis. Based on **reported compliance**, 63% (n=47) of controls and 46% (n=35) of intervention participants completed their treatment as allocated when missing diary entries were set to 0 min PA/day, and 53% (n=40) of interventions when participant's yearly PA mean was used, respectively. Based on **assumed compliance** (improvement in Watt performance), 76 (50%) behaved as controls (42 from control, 34 from intervention group), 36 (24%, 18 from each group) as participants of the intervention group, and 39 (26%) could not be allocated due to missing information on Watt performance change (19 dropouts, 3 declined test, 17 with invalid max/submax categorization). Dose-response analysis was based on complete cases set. For the **explorative subgroup analysis**, 130 participants had complete data on trabecular BMD, while 62 (48%) were intervention participants (thereof 10 CCS with a z-score ≤-1 at baseline).

Effects of exercise on bone parameters

Neither **ITT with LOCF** (**Table 2** and **Fig 2**, primary analysis) nor **complete case analysis** (**Supplementary Table 1**) revealed statistically significant differences from T0 to T12 between intervention and control group for any bone measurements. Pre-specified **PP** with **reported compliance** (online-diary based; **Supplementary Table 2-5**) showed a significant larger increase in

femoral neck BMD by 0.013-0.015g/cm^2 (corresponds to 1.6-1.8%) for LOCF and complete case analysis comparing the intervention to the control group. **PP** with **assumed compliance** (CPET peak Watt performance based; **Supplementary Table 6**) revealed a significant larger increase in trabecular BMD by 3.597 mg/cm^3 (1.5%) comparing the intervention to the control group. Dose response analysis (**Supplementary Table 7**) did not show significant intervention effects. The **exploratory subgroup analyses** showed that trabecular BMD increased by 6.848 mg/cm^3 (2.8%) more in intervention participants starting at low trabecular BMD (z-score ≤-1) compared to those with BMD z-score >-1 (**Table 3**).

DISCUSSION

This novel RCT that investigated the effect of a tailored one year exercise program for adolescent and adult CCS (n=151, 44% female) on lower body bone parameters as secondary outcome in the SURfit study found no effects in its primary ITT analysis. Nevertheless, predefined per protocol analyses found that CCS who *reported compliance* to the intervention significantly improved femoral neck BMD by 1.6% to 1.8% more than controls. Likewise, those with *assumed compliance* improved distal tibia trabecular BMD by 1.5% more than their counterparts. Based on further exploratory analysis, intervention group participants starting at low trabecular BMD (z-score <-1)[25] improved their density by 2.8% more than those starting with BMD z-scores >-1. Our general and individualized exercise program, not specifically designed to promote bone health, may therefore not be sufficient to promote bone density and structure of lower body bones.

This paper's null results may be due to the exercise program of SURfit that mainly included aerobic exercise aimed and powered to improve predominantly its primary endpoint of cardiovascular disease risk, and only secondarily affecting bone health.[20] Although a considerable number of CCS showed low BMD,[27] the majority of CCS in this study were in the normal range comparable to healthy adults.[28] Nevertheless, bone health of CCS can benefit from PA when being exposed already to a relatively low number of high mechanical impact peaks (roughly 300 impact repetitions/day e.g. from jumping, running)[27] rather than through low impact training (e.g. walking, cycling, swimming).[27,29-33] Most CCS probably failed reaching this threshold within our individual PA program and thus, the program was not optimal to boosting bone remodeling. Our exercise program may have been more efficient if started earlier, as bone remodeling to physical loading is generally more prominent in younger, still growing CCS.[30,32,34,35]

Our one year program was based on a carefully established concept that focused on different motivational tools to optimize intervention adherence.[20] Still, exercise adherence during and post cancer treatment is challenging and is more difficult to reach in long-term than short-term programs.[12,36] Making personal PA goal attainment even more complicated, CCS often show a long history of low PA often introduced during cancer therapy.[1,2,4,5,37] To change long-term habits for a period of one year might thus have been a motivational barrier for participating CCS. Indeed, only 46% of the intervention group reported a predefined two-thirds compliance of the expected training (≥100 min of addition intense PA/week). This may be an important reason why exercise trials are often unsuccessful at achieving clinically meaningful increases in bone health.[19] These findings suggest a compliance problem in the intervention group and contamination within the control group, which is a well-known phenomenon in behavior-based RCTs that are based on self-selection.[38,39]

We found an intervention effect on trabecular BMD of the femoral neck and distal tibia in those compliant compared to the non-compliant group. Even though all included CCS were willing to increase their weekly exercise workload, only 1 out of 2 documented enough exercise hours, and only 1 out of 4 of the intervention group increased their peak performance within one year. Moreover, 24% of controls increased their peak exercise performance which is a clear sign that these control group participants did indeed train against our agreement.

Improving bone health is especially important for those CCS who show low BMD already at a young age, a risk factor for osteoporosis and increased risk of fracture later in life.[1,2] In accordance with a similar trial among child CCS,[18] intervention group participants with low trabecular BMD at baseline improved more than those without osteopenia. Trabecular bone adapts its structure faster to changes in mechanical stimulation than cortical bone[40]. Cortical BMD temporarily decreases during the remodeling process before it can be mineralized.[41] Hence, this improvement in trabecular bone might

indicate the potential for a possible improvement in bone health with a more physically active lifestyle over a one-year period. This improvement in the architectural structure of bone is clinically relevant as it can be translated to a reduction in fragility fracture risk,[32,42] especially once BMD reaches the osteoporotic fracture threshold.[30,32] Comparable to our results, a BMD increase of 2% was sufficient in delaying this fracture threshold by several years.[42] It is promising that especially those starting the training with osteopenia, or in other words who need it most, experienced the largest benefits from the study.

Strength and limitations

Strengths of our study include: it is one of the first exercise trial with a RCT design in a relatively large population of CCS, and the objective measures of bone densitometry and architecture by two methods (DXA and pQCT) were performed by trained staff at one single center. Assessors conducting DXA measurements and determining bone parameters were blinded. The program duration of one year was sufficient to allow for sustained changes in behavior, and in parallel to stimulate sufficient bone remodeling to detect clinically relevant effects on bone structure.[43,44]

The major limitation is that the intervention was not mainly tailored to improve the secondary outcome of bone health, but rather cardiovascular health and therefore focused on a general exercise program. Only a minority of our adult CCS showed low bone mass for which clinical improvement is recommended.[28] Results from the per-protocol and exploratory analyses need to be interpreted carefully since they are prone to false positive findings and generally would need to be adjusted for pre- and post- randomization prognostic factors and multiple testing.[45] Sport adherence was based on self-declaration which is prone to desirability bias by over-reporting.[38] Lastly, the larger dropout rate in the intervention group (17% vs. 8% in controls), the cross-contamination of the control group, although common in such RCTs and the nature of the general exercise program might have contributed

to the ITT based null effects. Reduced efficiency may have also arisen from the large heterogeneity of our study population for tumor history and levels of PA.

Conclusion

To our knowledge, this is the first RCT with CCS investigating lower body bone health in an individualized one year exercise program. In the presence of only a small number of CCS with low BMD, there were no statistically and clinically significant differences between intervention and control group for changes in lower body bone parameters measured by DXA and pQCT in our primary analysis. Despite the overall null effects, we found weak evidence that our exercise program may have been beneficial for some clinically relevant bone parameters in the range between 1.5 to 2.8% in compliant participants and those with initial osteopenia. Nevertheless, our one year individual PA intervention may not have been specific and attractive enough to affect lower body bone health in young adult CCS two decades after cancer diagnosis. Thus, further studies should focus on younger, preferably still growing youth, predominantly on populations at risk with BMD z-score≤-1, and on CCS during or shortly after treatment where the potential for bone adaptation is highest. Intervention programs should apply bone specific exercises that include high impact, bending and torsional forces known to strain bone with a layout that is attractive enough to maximize compliance.

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Ethics statement: The study was approved by the Swiss Ethics Committee on research involving humans (Ethikkommission Nordwest- und Zentralschweiz). Written informed consent was obtained from each survivor prior to participation. Data was pseudonymized and safely stored compliant to data protection laws.

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FIGURE LEGENDS

Fig. 1. CONSORT Diagram.

Fig. 2. Adjusted marginal mean differences between the intervention and control group from baseline to 1-year follow-up for densitometric and architectural bone parameters (adjusted for sex, tumor type, bone parameters at baseline, and age). Effects were estimated by ANCOVA models using an intention-to-treat approach (missing items were imputed by last observation carried forward). Effect estimates with 95%-CI are expressed as unstandardized beta for DXA z-scores (age and gender matched norms [23]) and as z-standardized beta coefficients for pQCT (in order to compare all estimates in the same figure). Positive effects indicate changes in favour of the intervention group. Abbreviations: BMD, Bone mineral density; CSA, Cross-sectional area; DXA, Dual-energy X-ray absorptiometry; pQCT, Peripheral quantitative computed tomography; SSI, Strength-strain index; T4, Distal epiphysis (4%) of the tibia; T66, diaphysis (66%) of the tibia.

TABLES

Table 1. Baseline characteristics of the SURfit study participants (n = 151)

	Intervention (n = 76)	Control (n = 75)
Basic characteristics		
Sex, female	33 (43%)	33 (44%)
Age at study (yrs.)	31.5 (8.3)	29.3 (8.7)
Height (cm)	170.1 (8.9)	171.3 (9.7)
Weight (kg)	71.0 (15.3)	70.0 (15.5)
Body composition		
BMI (kg/m^2)	24.4 (4.3)	23.7 (4.0)
DXA lean body mass (kg)	46.7 (10.1)	46.1 (9.6)
DXA fat mass (kg)	22.6 (6.6)	21.9 (6.8)
pQCT tibia 66% muscular CSA (mm^2)	6176 (1104)	6076 (1212)
Cancer related information		
Age at diagnosis (yrs)	7.6 (5.1)	7.3 (4.6)
Time since diagnosis (yrs)	24.0 (8.5)	22.0 (9.2)
ICCC-3 cancer diagnoses		
I Leukemia	24 (32%)	31 (41%)
II Lymphoma	18 (24%)	14 (19%)
III Central nervous system tumors	11 (14%)	6 (8%)
VIII Malignant bone tumors	2 (3%)	3 (4%)
IX Soft tissue and other extraosseous	8 (11%)	3 (4%)
Other tumors	13 (17%)	18 (24%)
Chemotherapy		
Received anthracycline therapy	45 (59%)	51 (68%)
Cumulative dose (mg/m^2) [1]	192 (89)	194 (98)
Received steroid therapy	42 (55%)	45 (60%)
Cumulative dose (mg/m^2) [1]	4046 (3431)	4443 (3172)
Radiation therapy		
Received cranial radiation therapy	12 (16%)	15 (20%)
Cranial radiation dose ≥24 Gy	10 (13%)	10 (13%)
Stem cell transplantation	5 (7%)	4 (5%)
Health behaviour		
MVPA (min/day) [2]	38 (20)	43 (20)
Smoker, yes	19 (25%)	16 (21%)
Vitamin D Supplement, yes (within last 3 months)	8 (11%)	5 (7%)
Calcium Supplement, yes (within last 3 months)	5 (7%)	3 (4%)
Duration of trial		
Duration (weeks)	56.4 (3.5)	56.3 (3.5)

NOTE. Data are presented as n (%) / Mean (SD)
Abbreviations: CSA, cross-sectional area; DXA, dual-energy X-ray absorptiometry; ICCC-3, international classification for childhood cancer – third edition; MVPA, moderate to vigorous physical activity; pQCT, peripheral quantitative computed tomography.
[1] In those who received therapy.
[2] Determined by ActiGraph® GT3X+ accelerometer
Number of participants included (Intervention/Control): DXA: n=74/73; pQCT: n=71/71; Physical Activity: n=62/67; Smoker: n=76/73; Vitamin D Supplement: n=74/72; Calcium Supplement: n=74/71.

Table 2. Intervention effects on bone parameters from primary analysis (intention-to-treat with last observation carried forward)

	Intervention		Control		Adjusted difference at 12 months	
	Baseline	12 months	Baseline	12 months	Beta (95% CI)	p-value
DXA						
Femoral Neck BMD (g/cm^2)	0.83 (0.11)	0.84 (0.10)	0.85 (0.13)	0.85 (0.13)	0.007 (-0.002 to 0.017)	0.12
Hip BMD (g/cm^2)	0.95 (0.10)	0.96 (0.10)	0.96 (0.12)	0.96 (0.12)	0.002 (-0.006 to 0.010)	0.65
Lumbar Spine BMD (g/cm^2)	1.00 (0.11)	1.00 (0.11)	1.00 (0.11)	1.01 (0.11)	-0.003 (-0.011 to 0.005)	0.44
pQCT						
T4 Total BMD (mg/cm^3)	304.1 (35.1)	305.5 (35.2)	305.1 (39.7)	305.1 (39.1)	1.209 (-0.717 to 3.136)	0.22
T4 Trabecular BMD (mg/cm^3)	240.9 (31.6)	242.3 (31.4)	240.4 (35.5)	240.2 (34.6)	1.731 (-0.421 to 3.882)	0.11
T66 Cortical BMD (mg/cm^3)	1136.0 (26.4)	1136.6 (26.3)	1139.5 (26.6)	1141.3 (26.0)	-0.539 (-2.649 to 1.572)	0.62
T66 Cortical CSA (mm^2)	319.6 (51.6)	320.5 (51.4)	312.8 (45.8)	314.0 (46.2)	-0.004 (-1.107 to 1.098)	0.99
T66 SSI (mm^3)	2223.9 (513.2)	2227.4 (515.9)	2152.0 (498.7)	2160.5 (485.7)	-0.794 (-19.373 to 17.785)	0.93

NOTE. Intention-to-treat analyses with last observation carried forward. Group differences were analyzed using analysis of covariance (ANCOVA) adjusted for age, sex, tumor type, and baseline bone. Data are presented as means (SD).
Abbreviations: BMD, bone mineral density; CSA, cross-sectional area; DXA, dual-energy X-ray absorptiometry; pQCT, peripheral quantitative computed tomography; SSI, strain strength index; T4, Tibia 4% (distal epiphysis); T66, Tibia 66% (diaphysis).
Number of participants included in analyses (Intervention/Control): Femoral Neck and Hip BMD: n=75/72; Lumbar Spine BMD: n=74/72; Tibia 4%: n=76/74; Tibia 66%: n=73/72.

Table 3. Explorative subgroup analyses comparing intervention participants showing low (z-score ≤-1) vs. normal bone mineral density (z-score >-1)

	Beta (95% CI)	**p-value**
DXA		
Femoral Neck BMD (g/cm^2)	0.006 (-0.019 to 0.030)	0.83
Hip BMD (g/cm^2)	0.001 (-0.023 to 0.025)	0.99
Lumbar Spine BMD (g/cm^2)	-0.006 (-0.024 to 0.011)	0.65
pQCT		
T4 Total BMD (mg/cm^3)	-0.757 (-5.361 to 3.847)	0.91
T4 Trabecular BMD (mg/cm^3)	**6.848 (0.470 to 13.226)**	**0.03**

NOTE. Exploratory subgroup analyses were performed for bone parameters of intervention participants showing low BMD (z-score ≤-1) compared to those starting at BMD z-score >-1 at baseline by adding an interaction term between group allocation and low baseline BMD to the analysis. Data are presented as mean (SD).
Abbreviations: BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; pQCT, peripheral quantitative computed tomography; T4, Tibia 4% (distal epiphysis).
Number of participants included in analyses (Intervention-low BMD/Control-low BMD): Femoral Neck: n=62-13/76-18: Hip BMD: n=62-7/76-12; Lumbar Spine BMD: n=61-22/66-22; Tibia 4%: n=62-26/68-31; Tibia 66%: n=62-10/68-17.

Survivors of childhood cancer have increased vulnerability later in life to decreased bone mineral density (BMD) and fractures. Here, the authors tested whether a one-year exercise program could help improve lower-body bone health among 151 cancer survivors, age 16 and up. Those randomized to the exercise group performed an additional 2.5 hours of intense physical activity each week, while those in the control group continued their usual exercise habits. Bone mineral density was measured in the lumbar spine, hip, femoral neck, and tibia. After 12 months, the researchers found no statistically or clinically significant difference between the two groups.