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THE ROLE OF EXERCISE AT IMPROVING BONE HEALTH IN YOUNG PEDIATRIC CANCER SURVIVORS

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Luis Gracia Marco

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THE ROLE OF EXERCISE AT IMPROVING BONE HEALTH IN YOUNG PEDIATRIC CANCER SURVIVORS

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TABLE OF CONTENTS

RESEARCH PROJECTS AND FUNDING 20

LIST OF ABBREVIATIONS 21

ABSTRACT 23

RESUMEN 24

GENERAL INTRODUCTION 25

Chapter 1. Exercise and bone health in young pediatric cancer survivors 26

AIMS AND HYPOTESHES 38

MATERIAL AND METHODS 41

Chapter 2. Methodological overview of the systematic review and meta-analysis 42

Chapter 3. Methodology and design of the iBoneFIT randomized controlled trial 43

RESULTS AND DISCUSSION 63

Chapter 4. Effect of exercise on bone health in children and adolescents with cancer during and after oncological treatment: A systematic review and meta-analysis 64

Chapter 5. Determinants of bone parameters in young paediatric cancer survivors: The iBoneFIT Project 99

Chapter 6. Lean mass attenuates negative associations of watching television with bone parameters in young paediatric cancer survivors 126

Chapter 7. Every move counts to improve bone health at clinical sites in young pediatric cancer survivors: the iBoneFIT project 149

Chapter 8. Muscle strength deficits are associated with low bone mineral density in young paediatric cancer survivors: The iBoneFIT project 176

Chapter 9. Comorbid sarcopenia and low bone mineral density in young pediatric cancer survivors 215

Chapter 10. Effects of a 9-month online resistance exercise intervention on bone health in young pediatric cancer survivors: A Randomized Controlled Trial 245

GENERAL DISCUSSION 275

Chapter 11. An integrative discussion of the International Doctoral Thesis 276

CONCLUSIONS 297

Chapter 12. Conclusions of the International Doctoral Thesis 298

FUTURE PERSPECTIVES 302

Chapter 13. Future perspectives 303

ANNEXES 304

Chapter 14. Manuscripts derived from the present International Doctoral Thesis 305

LAST PAGE 314

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List of abbreviations

aBMD: Areal bone mineral density.

ALMI: Appendicular lean mass index.

ANCOVA: Analysis of covariance.

BM: Body mass.

BMAD: Bone mineral apparent density.

BMC: Bone mineral content.

BMI: Body mass index.

BPAQ: Bone-specific physical activity questionnaire.

CDI: Children Depression Inventory.

CERT: Consensus on Exercise Reporting Template.

CG: Control group.

CIs: Confidence intervals.

CMJ: Countermovement jump.

CONSORT: Consolidated Standards of Reporting Trials.

DAG: Directed acyclic graph.

DXA: Dual energy X-ray absorptiometry.

ESs: Effect sizes.

FN: Femoral neck.

HRpeak: Heart rate peak.

HSA: Hip Structural Analysis.

ICC: Intraclass correlation coefficients.

IFIS: International Fitness Scale.

IG: Intervention group.

iMUDS: Instituto Mixto Universitario Deporte y Salud.

IQR: Interquartile Range.

LOT-R: Life Orientation Test-Revised.

LPA: Light physical activity.

LS: lumbar spine.

Min: Minutes.

MSAS: Minimum sufficient adjustment set.

MVPA: Moderate-to-vigorous physical activity.

NN: Narrow neck.

ORs: Odds ratios.

PANAS-C: Positive Affect Schedule for children.

PedsQLTM: Paediatric Quality of Life Inventory.

PHV: Peak height velocity.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

QCT: Quantitative computed tomography.

RAMP: Raise, activate, mobilise and potentiate.

RCT: Randomized controlled trial.

SAS: Statistical Analysis System.

SB: Sedentary behaviors.

SD: Standard deviation.

SDS: Standard deviation scores.

SE: Standard errors.

SHS: Subjective Happiness Scale.

SJ: Squat jump.

sBMD: Surface bone mineral density.

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.

SPSS: Statistical Package for the Social Sciences.

STAIC-T: State-Trait Anxiety Inventory for Children.

STROBE: Strengthening The Reporting of OBservational Studies in Epidemiology.

TBS: Trabecular Bone Score.

TV: Television.

vBMD: Volumetric bone mineral density.

VIF: Variance inflation factor.

WB: whole body.

WK: Week.

YAP: Youth Activity Profile.

Abstract

Resistance exercise of high impact loading has emerged as a potential non-pharmacological intervention to improve bone health. However, its impact on young pediatric cancer survivors is still not elucidated. The overall aim of the present International Doctoral Thesis is to assess the impact of resistance exercise of high impact loading and movement behaviors on bone health in young pediatric cancer survivors, exploring key factors influencing bone health. Firstly, this thesis aims to investigate whether previous exercise interventions were effective at improving bone health in children and adolescents with cancer during and after oncological treatment (**Chapter 4)**. Furthermore, it seeks to evaluate the relationship between sedentary behaviors (SB), physical activity, lean mass and muscle function with bone health in young pediatric cancer survivors (**Chapter 5-9**). Lastly, it evaluates the efficacy of a 9-month online resistance exercise intervention of high impact loading on bone health in this population (**Chapter 10**).

The results of this thesis indicate that prior exercise interventions were not appropriate and therefore, ineffective to illustrate any beneficial effect on bone health (**Chapter 4**). Lean mass is consistently the most important positive determinant of most bone parameters (**Chapter 5**), and attenuates to the null the negative association between television (TV) watching time and most bone parameters in peri/post-pubertal survivors (**Chapter 6**). Additionally, the predicted associations of moderate-to-vigorous physical activity (MVPA) with higher areal bone mineral density (aBMD) are significant at most sites in pre-pubertal young pediatric cancer survivors (**Chapter 7**). Moreover, muscle strength deficits are prevalent in young pediatric cancer survivors and such deficits are associated with lower aBMD Z-score at all sites (**Chapter 8**). Over one-third of young pediatric cancer survivors present sarcopenia confirmed, and have significantly higher risk of low aBMD Z-score at total body, total hip and femoral neck, than those without sarcopenia (**Chapter 9**). Lastly, a 9-month online resistance exercise intervention of high impact loading does not increase femoral neck aBMD Z-score, yet it induces improvements at the bone health of the hip region in young pediatric cancer survivors (**Chapter 10**).

Based on the findings of this International Doctoral Thesis, avoiding an abnormal body composition, unhealthy lifestyle, physical fitness deficits and doing resistance exercise intervention of high impact loading could be linked to improved bone health after pediatric cancer.

Resumen

El ejercicio físico de fuerza y alto impacto ha surgido como una posible estrategia no farmacológica para mejorar la salud ósea. Sin embargo, aún no se ha demostrado si podría mejorar la salud ósea de jóvenes supervivientes de cáncer. El objetivo general de la presente Tesis Doctoral Internacional es evaluar el impacto del ejercicio físico de fuerza y alto impacto, y los comportamientos del movimiento en la salud ósea de jóvenes supervivientes cáncer, explorando factores clave que influyen en la salud ósea. En primer lugar, esta tesis tiene como objetivo evaluar si las intervenciones de ejercicio físico previas han sido efectivas para mejorar la salud ósea de niños y adolescentes con cáncer durante y después del tratamiento oncológico (**Capítulo 4**). Asimismo, evalúa la relación entre los comportamientos sedentarios, actividad física, masa magra y función muscular con la salud ósea en jóvenes supervivientes de cáncer (**Capítulo 5-9**). Por último, tiene como objetivo evaluar la eficacia del ejercicio físico de fuerza y alto impacto sobre la salud ósea en esta población (**Capítulo 10**).

Los resultados de esta tesis indican que las intervenciones de ejercicio física previas no fueron apropiadas y por tanto, ineficaces para mostrar cualquier efecto beneficioso sobre la salud ósea (**Capítulo 4**). La masa magra es consistentemente el determinante positivo más importante de la mayoría de los parámetros óseos (**Capítulo 5**) y tiene un factor protectivo ante la asociación negativa entre el tiempo de televisión y la mayoría de los parámetros óseos en los supervivientes de cáncer peri/postpuberales (**Capítulo 6**). Además, las asociaciones de la actividad física moderada-vigorosa con densidad mineral ósea son significativamente positivas en la mayoría de las regiones en jóvenes supervivientes de cáncer prepuberales (**Capítulo 7**). Los déficits de fuerza muscular son prevalentes en jóvenes supervivientes de cáncer y dichos déficits se asocian con una baja densidad mineral ósea en todas las regiones (**Capítulo 8**). Más de uno de cada tres jóvenes supervivientes de cáncer presenta sarcopenia confirmada, teniendo así un riesgo significativamente mayor de tener una baja densidad mineral ósea en el cuerpo total, la cadera total y el cuello femoral, que aquellos sin sarcopenia (**Capítulo 9**). Por último, una intervención de ejercicio físico de fuerza y alto impacto en línea durante nueve meses de duración no es efectiva para aumentar la densidad mineral ósea del cuello del fémur, aunque se observan mejoras en la salud ósea de la región de la cadera en esta población (**Capítulo 10**).

Basándose en los hallazgos de esta Tesis Doctoral Internacional, evitar una composición corporal anormal, estilos de vida no saludables, déficits de fuerza muscular y realizar ejercicio físico de fuerza y alto impacto podría estar relacionado con una mejor salud ósea después del cáncer pediátrico.

GENERAL INTRODUCTION

Chapter 1. Exercise and bone health in young pediatric cancer survivors

Introduction

Cancer is commonly defined as the uncontrolled proliferation of cells of any body tissue that gradually acquire malignancy and evolutionary advantages [1]. This lack of control in normal cellular processes is mainly caused by different genetic mutations [2]. Pediatric cancer usually has an embryonic origin, in tissues such as the central nervous system, bone marrow, bones, muscles or the sympathetic nervous system. Around 10% of all pediatric cancer diagnoses in children and adolescents can be inherited by pathogenic variants in specific genes that increase cancer predisposition [3]. In addition, the interaction of children with the environment can also produce mutations in the genetic code that predispose them to develop cancer. Certain exposures such as passive cigarette smoke [4], and ultraviolet radiation from the sun [5] increase the risk of developing genetic alterations. The environmental causes of pediatric cancer have been particularly difficult to identify not only because cancer in children is rare, but also because it is difficult to determine what children might have been exposed during their early development.

Pediatric cancer is one of the main causes of mortality in childhood and adolescence [6]. In children from one to 14 years, it is the second cause of death after accidents, while in adolescents from 15 to 19 years, it is the fourth cause of death [6]. Although it is considered as a rare disease due its relative low incidence worldwide [6], it has remarkably increased in recent decades. In Spain, the current incidence has reached unprecedent rates close to 1,000 diagnoses per year according to the last update of the Spanish Registry of Children with Tumors [7], with leukemia, cancer of the central nervous system and lymphoma being the most common [8]. Nevertheless, the survival has also experienced a significant increase with a 5-year survivorship rate of 82% in Spain among all pediatric cancer diagnoses (**Figure 1**) [7]. Madrid and Barcelona represent the two main provinces in which pediatric cancer is commonly diagnosed reaching 22.9% and 16.1% of new cases respectively, from 2018 to 2022 [7]. Interestingly, pediatric cancer diagnosis is slightly higher in males (54.6%) than in females (45.4%), and also in children aged from one to four years old than those younger or older [7].

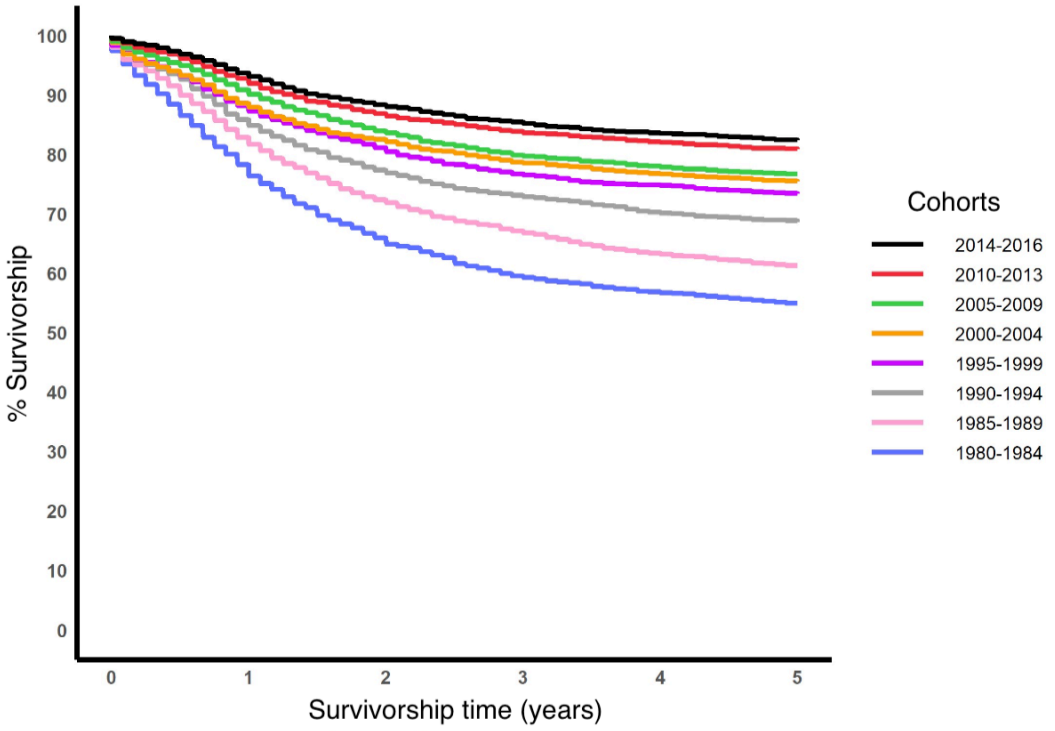

Figure 1. Percentage of survivorship of pediatric cancer in Spain from 1980 to 2016. Retrieved from the Spanish Registry of Children with Tumors [8].

Pediatric cancer treatments and poor bone health

During the last decades, the considerable increase in the 5-year survival rate has mainly been not only due to early diagnoses, but also because of the wide variety of anticancer combined modalities and the introduction of personal and targeted medicine [9]. Yet, current therapies often cause serious consequences in those that survive and therefore, it is essential to obtain less aggressive treatments maintaining same survival rates. The intensive multimodal treatments received at very young ages to cure pediatric cancer interfere with normal growth and skeletal development [10-12]. Low aBMD, defined by age-, sex-, and race-specific aBMD Z- scores less than -1.0 (in comparison to reference healthy population), has been identified in up to two-thirds of pediatric cancer survivors [13]. Bone mass recovery does not always occur, even more than 20 years after treatment completion [14]. The pathogenesis of low aBMD in pediatric cancer survivors is multifactorial (**Figure 2**) [15] since the disease, its therapies, treatment-related systemic disorders (i.e., primarily endocrinopathies), nutritional deficits and lifestyle factors (i.e., immobilizations, physical activity limitations) that are usually experienced by pediatric cancer survivors, also affect bone health [15]. All these components impair the attainment of peak bone mass gain during childhood and adolescence which is fundamental for later aBMD in life [15].

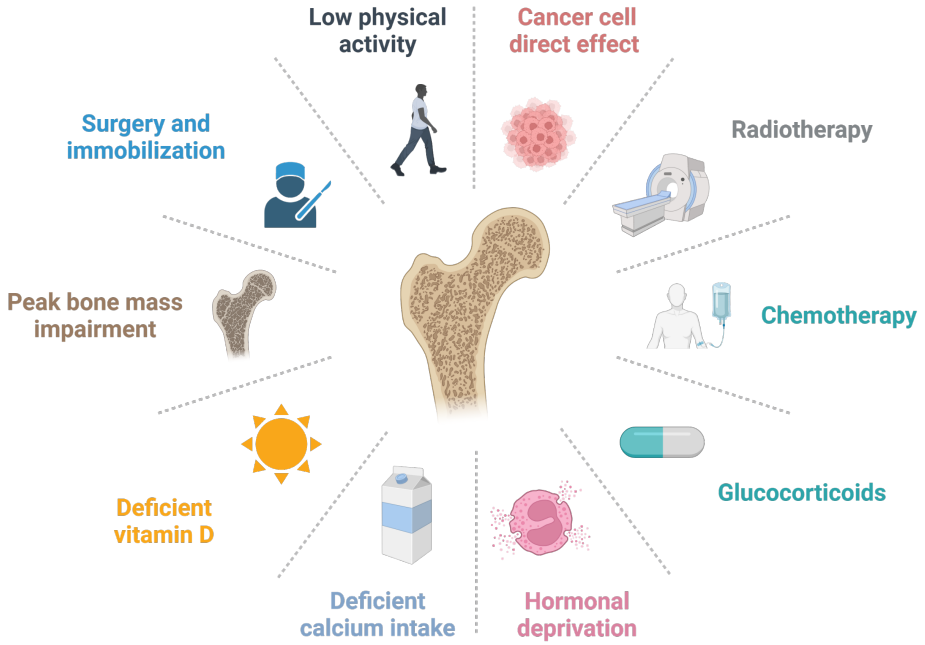

Figure 2. Risk factors of poorer bone health in pediatric cancer survivors. Adapted from Marcucci et al. [15].

Chemotherapy has been one of the most studied treatments thus far. In the 1940s, Alfred Gilman and Louis Goodman began clinical studies against lymphoma using mustard gas, laying the foundation for the use of chemotherapy against cancer [16]. Since this milestone, constant progress has been made in the creation of drugs whose main objective has been to control cell proliferation. Most common side effects of chemotherapy include encephalopathy, cerebellar degeneration, myelopathy, and impairments on vision, hearing and taste. These effects can be aggravated by co-administration of chemotherapy agents or combination with other therapies such as radiation [17]. Methotrexate, an anti-metabolite used in numerous treatment regimens for pediatric cancer, is associated with low aBMD and fractures in pediatric cancer survivors [18]. The administration of methotrexate may induce early chondrocyte (cartilage cells) apoptosis, inhibit osteoblast proliferation while might also increase osteoclast activity and bone resorption [19,20]. Glucocorticoids are also used to treat many pediatric cancers, and have a direct suppressive effect on formation of the chondrocyte matrix and in turn, suppress the synthesis of local growth factors [21]. Moreover, other chemotherapy agents such as ifosfamide and cyclophosphamide have been shown to have adverse effects on bone health [12].

Radiotherapy has also been a key breakthrough in oncology, yet administered during growth in children it deserves special attention. Radiotherapy has been part of effective multimodality therapy for childhood acute leukemia since it was introduced in the late 1960s

[22]. This treatment consists of administering ionizing energy, either in the form of photons, X-rays or protons, to a tumor mass while preserving the rest of the surrounding tissues. However, the resulting radiation-associated late effects including disrupted growth and endocrine function are well recognized [23]. The main side effects are dependent of the irradiated region and the cumulative doses, and can differ depending on the survivorship stage. Direct damage to irradiated bones, gonadal insufficiency secondary to pelvic radiation and damage to the hormonal mechanisms of the hypothalamic-pituitary axis have been indicated as risk factors for low aBMD [24]. Children with brain tumors, and those with other diagnoses who received cranial radiation as part of therapy, are particularly vulnerable [25].

Bone development in healthy children and adolescents

Normal bone mineralization follows skeletal development, progressing throughout childhood, peaking in adolescence (**Figure 3**) [26], and tapering off in early adulthood [26]. During the second decade of life, up to 95% of total bone mass is acquired [10], and therefore failure to attain sufficient bone mass during this stage may result in either persistent decrements in aBMD, or in the early development of adult onset osteoporosis. During childhood, long bones lengthen by interstitial growth of the epiphyseal plates. Chondrocytes in the epiphyseal plate rapidly proliferate, organize themselves into long columns, and push the epiphysis away from the diaphysis [27]. Chondrocyte division slows down toward the end of adolescence, the epiphyseal plates become thinner and thinner until eventually, they are replaced by bone. This process creates a structural matrix for calcification and lengthens the bone. Osteoblasts, originated from mesenchymal stem cells, just below the periosteum secrete bone matrix on the external surface of bone [28].

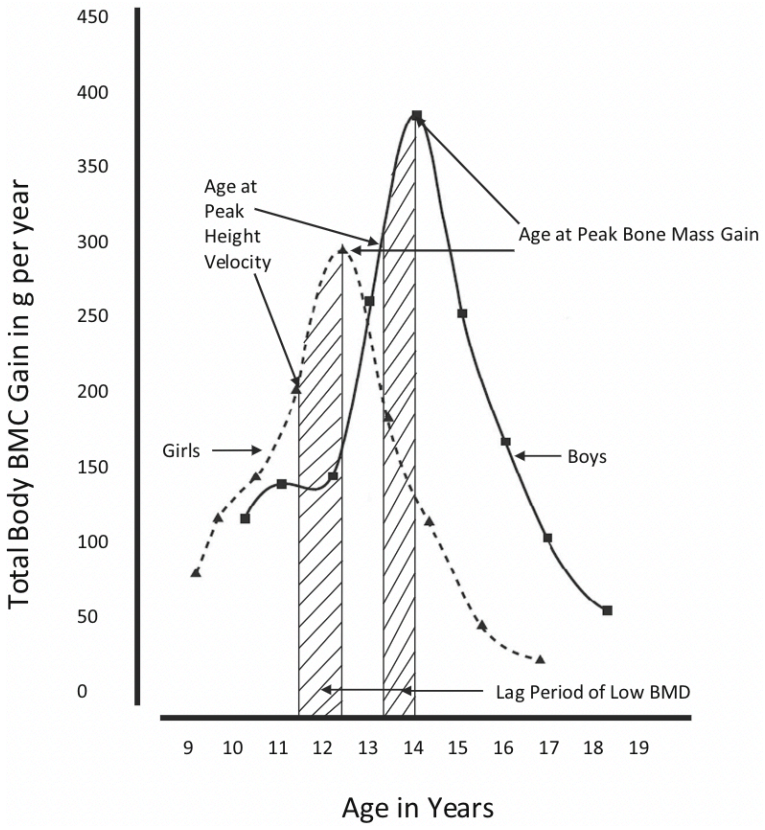

Figure 3. Peak bone mass development. Retrieved from Weaver et al. [26].

Bone mineralization depends both on internal homeostatic mechanisms and external mechanical strain for structural integrity and strength [28]. About 80% of peak bone mass is genetically determined, but hormone levels, the environment, and certain lifestyle factors can also influence bone accrual [26]. Growth hormone and insulin like growth factor-1 promote bone turnover by stimulating osteoblast proliferation and differentiation [29]. Adrenal androgens and its metabolites also contribute to bone mass by upregulating the osteoprotegerin receptor activators of NF-κB ligand osteoblasts which inhibit osteoclast resorption [30]. Children require sufficient calories as well as adequate calcium intake [31] and vitamin D status [32] to provide the energy and minerals necessary for bone growth. Previous research has demonstrated that calcium supplementation increases aBMD [33], and that serum 25-hydroxyvitamin D (25(OH)-D) levels are strongly correlated with aBMD in children [34]. Bone remodeling is also stimulated by mechanical strain as a result of applied external mechanical stress according to Wolff's law [35,36]. In this sense, the Mechanostat Theory suggests that bones adapt their integrity and structure depending on the mechanical stresses placed upon them. This adaptation occurs through a dynamic process of bone resorption (breaking down of bone tissue) and bone formation (building new bone tissue) [35-37]. These osteoblast-osteoclast interactions are necessary and must be coordinated in time and space to maintain the structural integrity.

Exercise, physical activity and bone health

When the human body moves, mechanical stresses are placed to bone in the form of muscular contraction, impact loading and gravitational forces [35,36], whereas decreases in mechanical strain (immobility or disability) result in bone resorption [38]. Therefore, resistance exercise of high impact loading can contribute to bone accrual during growth mass since the impacts produced against the ground of this exercise type causes higher forces on the bones and the needed stimulus for their development [39]. A recent systematic review has shown that plyometric jump training causes improvements in bone mineral content (BMC), aBMD and structural properties in children and adolescents [35]. More specifically, an 8-month jumping intervention (~3 min/day) improved bone mass in the proximal femur in pubertal children [36]. Mackelvie et al. [37] showed that a 7-month jumping intervention (10 min, 3 times/week) enhanced bone mass in the femoral neck and lumbar spine in pubertal girls. Additionally, Vlachopoulos et al. [38,39] found that a 9-month jumping intervention (10 min, 3 to 4 times/week) improved bone outcomes in adolescent males participating in non-osteogenic sports and with poorer bone health.

A similar osteogenic effect might be seen in pediatric cancer survivors. In addition to the dietary counseling and appropriate supplementation to assure adequate Vitamin D and calcium intake, the Children's Oncology Group Long Term Follow-up Guidelines recommend resistance exercise of high impact loading to improve bone health [40]. Pharmacologic interventions are also possible for those with very low aBMD or a history of multiple fractures (i.e., bisphosphonates) [41]. The use of bisphosphonates, which reduce bone turnover directly by decreasing the recruitment of osteoclasts and indirectly stimulating osteoblasts, requires careful and frequent monitoring by a qualified endocrinologist as these medications can cause some potential side effects such as fever, malaise, abdominal pain, vomiting, muscle or bone pain [42].

A previous randomized controlled trial (RCT) in children with acute lymphoblastic leukemia showed that resistance exercise was not effective at preventing aBMD reduction [40]. However, the intervention duration and volume were not properly described. Another RCT focusing on low-magnitude, high frequency mechanical stimulation seemed to improve total body aBMD in pediatric cancer survivors, while a reduction was observed in the placebo group [43]. Thus, it remains unknown whether resistance exercise of high impact loading could be effective at improving bone health in young pediatric cancer survivors.

In healthy children and adolescents, measured upper- and lower-body muscle strength have been consistently associated with total body [44, 45], upper [46,47] and lower [46,47] extremities BMC, and total body and femoral neck aBMD [48]. Similarly, in adult pediatric cancer survivors, Joyce et al. [49] found that upper- ($R^2 = 0.56$) and lower-body ($R^2 = 0.33$-0.40) muscle strength was positively associated with aBMD. Therefore, muscle strength increases could likely be associated with improvements in aBMD. However, in younger survivors, the literature describing these associations is scarce.

The international physical activity guidelines for pediatric cancer survivors underline the importance of engaging in at least an average of 60 min of MVPA per day and limiting SB [50,51]. A previous study showed significant correlations between self-reported physical activity levels and higher lumbar spine aBMD Z-score in 319 pediatric cancer survivors (14.5 ± 0.1 years old) [52]. However, the majority of pediatric cancer survivors do not reach these recommendations even years after treatment completion [53]. Previous research has reported that pediatric cancer survivors are remarkably inactive [54], more than their healthy peers [55]. Pediatric cancer survivors do not often receive the osteogenic benefits from resistance exercise of high impact loading and hence, properly powered, well-controlled clinical research is still needed to determine whether resistance exercise of high impact loading is effective at improving bone health in young pediatric cancer survivors.

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AIMS AND HYPOTESHES

Aims

The overall aim of this International Doctoral Thesis is to assess the impact of exercise and movement behaviors on bone health in young pediatric cancer survivors, exploring key factors influencing bone health. This overall aim is addressed by different specific objectives:

- Specific aim I: To determine the pooled effect of exercise interventions in children and adolescents with cancer during and after oncological treatment on bone health, and to explore factors influencing the response of the exercise intervention.

- Specific aim II: To provide novel insights of the contribution of independent predictors of bone parameters in young pediatric cancer survivors.

- Specific aim III: To investigate the role of lean mass in the association of TV watching time with bone parameters in young pediatric cancer survivors.

- Specific aim IV: To examine the associations of 24-hour movement behaviors with aBMD parameters at clinical sites in pre-pubertal and peri/post-pubertal cancer survivors using compositional data analysis.

- Specific aim V: To investigate the prevalence of muscle strength deficits and the associations with aBMD parameters in young pediatric cancer survivors.

- Specific aim VI: To evaluate aBMD differences and the risk of low aBMD according to sarcopenia status in young pediatric cancer survivors.

- Specific aim VII: To investigate the effects of a 9-month online exercise program on bone health in young pediatric cancer survivors.

Hypotheses

The main hypothesis of this International Doctoral thesis is that avoiding an abnormal body composition, unhealthy lifestyle, physical fitness deficits and doing resistance exercise of high impact loading would be linked to improved bone health. Specifically, we hypothesize that:

I. Exercise would have a positive effect on bone health among pediatric cancer survivors in those with longer interventions that involve resistance exercise of high impact loading.

II. Lean mass and years from peak height velocity (PHV) would be the most important contributors of bone parameters in young pediatric cancer survivors.

III. Higher lean mass would play an important role in the association of TV watching time with bone health in young pediatric cancer survivors.

IV. Higher physical activity levels and lower SB would be associated with aBMD parameters at clinical sites in pre-pubertal and peri/post-pubertal cancer survivors.

V. Muscle strength deficits would be prevalent in young pediatric cancer survivors, and such deficits would be associated with lower aBMD Z-score.

VI. Young pediatric cancer survivors with sarcopenia would have higher risk of low aBMD Z-score than those without sarcopenia.

VII. A 9-month online exercise program would be effective at improving bone health in young pediatric cancer survivors.

MATERIAL AND METHODS

This section includes two chapters:

(i) **Chapter 2** presents the overview of the systematic review and meta-analysis that identified the knowledge gap of this International Doctoral Thesis.

(ii) **Chapter 3** provides an overview of the rationale, design, and methodology of the REBOTA-Ex RCT (within the iBoneFIT project), which contributed to the baseline data for the analyses conducted in **Chapters 5-9**, as well as the longitudinal data for the analyses conducted in **Chapter 10**.

Chapter 2. Methodological overview of the systematic review and meta-analysis

This systematic review and meta-analysis aimed to synthesize the evidence regarding the effectiveness of previous exercise interventions on bone health in children and adolescents with cancer during and after oncological treatment. The systematic search was conducted in the MEDLINE (via PubMed), Web of Science and Scopus databases from November 2021 to January 2022. RCTs and non-RCTs reporting pre-post changes of the effectiveness of exercise interventions on dual energy X-ray absorptiometry (DXA) measured bone parameters in young population (1-19 years) during or after oncological treatment were included. Exclusion criteria were as follows: (1) studies including individuals older than 19 years old; (2) non-eligible publication types, such as review articles, editorials, comments, guidelines or case reports; (3) assessment of aBMD and BMC using other methods (i.e., computed tomography); and (4) studies published in any language other than English. The following data were retrieved from the original reports: (1) first author and year of publication; (2) country from which the data were collected; (3) study design; (4) sample characteristics (age, sample size, body mass index, height, weight, and type of cancer); and (5) the method used for measuring bone measurement characteristics (aBMD, volumetric BMD, bone mineral apparent density and BMC, including values for whole body, lumbar spine, and femoral neck) at baseline and at end of follow-up. Pooled effect sizes (ESs) and 95% confidence intervals (95%CIs) were calculated, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were accordingly followed. This systematic review and meta-analysis was previously registered in PROSPERO (CRD42022310876).

Chapter 3. Methodology and design of the iBoneFIT randomized controlled trial

Abstract

Objective. To investigate the effect of a 9-month online exercise program on bone health in paediatric cancer survivors. This study also examined the effect of the intervention on body composition, physical fitness, physical activity, calcium intake, vitamin D, blood samples quality of life and mental health.

Methods. A minimum of 116 participants aged 6 to 18 years were randomized into an intervention (n = 58) or control group (n = 58). The intervention group received an online exercise program and diet counselling on calcium and vitamin D. In addition, five behavior change techniques and a gamification design were implemented in order to increase the interest of this non-game program. The control group only received diet counselling. Participants were assessed on 3 occasions: 1) at baseline; 2) after the 9 months of the intervention; 3) 4 months following the intervention. The primary outcome was determined by DXA and the hip structural analysis (HSA), trabecular bone score (TBS) and 3D-DXA softwares. Secondary outcomes included anthropometry, body composition, physical fitness, physical activity, calcium and vitamin D intake, blood samples, quality of life and mental health.

Methods

The iBoneFIT study was a multicenter, parallel groups RCT (1:1) designed under the equivalence basis and registered in isrctn.com (Reference: isrctn61195625, 2 April 2020). This protocol was reported based on Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [(1)]. Eligible participants from two paediatric oncology units of Southern Spain were contacted, informed, and if consenting, enrolled into the study after a meeting (T− 1) (see recruitment section). Then, randomization was performed by an external partner who was independent of the participant recruitment and enrolment process (see randomization section). Assessments was conducted at baseline (T0) and after nine (T1) and thirteen (T2) months in the "Instituto Mixto Universitario Deporte y Salud" (iMUDS, University of Granada). After finishing the study, participants in the control group was offered the same online exercise program. A graphical description of the study design is shown in **Figure 1**.

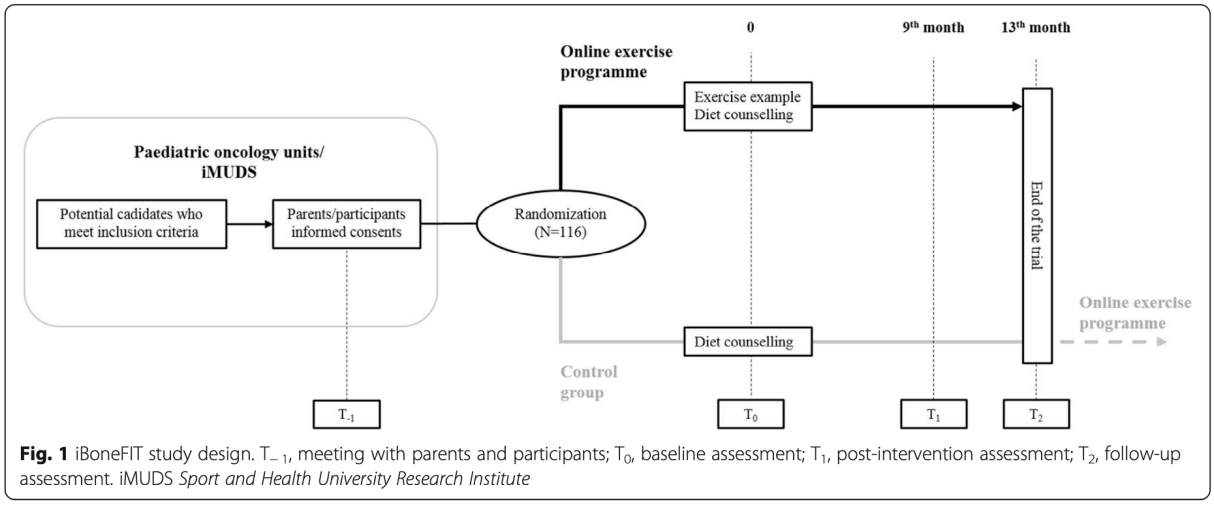

Fig. 1 iBoneFIT study design. T_ 1, meeting with parents and participants; T_0, baseline assessment; T_1, post-intervention assessment; T_2, follow-up assessment. iMUDS *Sport and Health University Research Institute*

Figure 1. iBoneFIT study design. T_{-1}, meeting with parents and participants; T_0, baseline assessment; T_1, post-intervention assessment; T_2, follow-up assessment. *iMUDS Sport and Health University Research Institute.*

Ethical approval

The study was performed following the ethical guidelines of the Declaration of Helsinki, last modified in 2013. This study was checked and approved by the Ethics Committee on Human Research of Regional Government of Andalusia (Reference: 4500, December 2019).

Inclusion and exclusion criteria

The iBoneFIT study included paediatric cancer survivors: 1) aged 6 to 18 years; 2) diagnosed at least 1 year earlier; 3) to have been exposed to radiotherapy and/or chemotherapy; and 4)

not currently receiving treatment for cancer. Exclusion criteria were defined as follows: 1) simultaneous participation in another study that place participants at any additional risk, discomfort or affect the results of both studies; 2) previous diagnosed anorexia nervosa/bulimia, known pregnancy and/or known alcohol and drug abuse; 3) children requiring chronic oral glucocorticoid therapy; 4) having an injury that may affect daily life activities and can be aggravated by exercise; and 5) to have a lower limb prosthesis that prevent bone assessment.

Recruitment

Eligible participants were contacted via telephone calls or information letters from the Units of Paediatric Oncology of the 'Virgen de las Nieves' (Granada) and 'Reina Sofía' (Córdoba) University Hospitals in Southern Spain. A short study information brochure was used in routine check-ups. Meetings were held with potential participants and parents/tutors to carefully inform about the benefits and risks of the study, and researchers answered any question that they had. Then, informed consents were given, and participants were given 15 days to send it to the researchers. A hotline was available to clarify remaining questions about the study. Those who did not react to the study invitation were followed up via phone call at the end of these 15 days in order to check if they wished to participate. All participants signed the informed consent before their visit to the iMUDS.

Randomization and blinding

Randomization to an intervention group (online exercise program, IG) or control group (no treatment, CG) was performed by an external partner who was independent of the participant recruitment and enrolment process, stratified by age and sex. Each participant was provided a uniform (0, 1) random number using the Statistical Analysis System (SAS) software, version 9.1 (SAS Institute Inc), within their respective age and sex group. Assignments were blinded to the assessors until all tests were completed. For feasibility reasons, the study was conducted in two waves of 58 children at most.

Sample size

We used femoral neck aBMD as the outcome to calculate the sample size, since it is a key variable in the diagnosis of osteoporosis. Since the study included children and adolescents (6-18years), the sample size was calculated taking into account that sub-group analysis by age groups (6 to 11 years and 12 to 18 years) may be required. Based on an expected effect size of

0.25 for the change in femoral neck aBMD, an α level of 0.05 and a power of 80%, a minimum of 116 participants was required (IG = 58 and CG = 58). This included a 20% extra for occasional losses and refusals and 10% for multivariable analyses. Calculations were obtained using G*Power (v.3.1.9.2) with analysis of variance: repeated measures (within-between interactions) for 2 groups (between factors) and 2 time points (pre, post, within factors). A correlation between measures of 0.7 was assumed, which is achievable when measuring bone outcomes [(2)].

Statistical analysis

All variables were checked for normality using both statistical and graphical methods. Results were presented as frequencies and proportions with 95% confidence intervals for categorical variables and mean (standard deviation [SD]) or median (range) for continuous variables. A descriptive analysis of the participants characteristics was performed as soon as the baseline assessments were completed. This cross-sectional analysis showed the comparability of IG and CG and the need for adjustment when between group comparisons were done.

General Lineal Models was used to examine the training effects [time (pre-post 9-month intervention) x group interaction] on the primary and secondary outcomes. Change in bone outcomes was used as age and sex-adjusted Z-scores. The baseline level of each outcome variable was entered as covariate. Effect sizes were reported. Multiple imputation methods and sensitivity analysis (i.e., propensity score) were performed to handle missing data and appreciate the potential influence of missing responses. Finally, statistical analysis was carried out by per-protocol and intention-to-treat approaches.

Participant adherence and compliance

Participants were allowed to withdraw at any time; nevertheless, several strategies were used for adherence and compliance with the intervention. The minimum compliance allowed at each phase of the intervention was 50% but the overall compliance after 9 months had to reach 70%. A lack of compliance (<50%) without justified reasons in the first phase of the intervention resulted in the participant being invited to drop out from the study. This 70% adherence rate meant completing 95 sessions of 136. If a participant did not complete 70% of the intervention by the end of the 9 months but could reach 70% within two additional weeks, the exercise program was extended for them. Compliance with the intervention was monitored using a diary and it was sent to the research staff on a monthly basis (Item 5). Parental involvement was requested for this matter.

Participants and their parents were verbally motivated to participate in the intervention and to attend to all the assessments. Children who completed successfully the intervention received a certificate of achievement. Children were the key part of this study, and they deserve acknowledgements for their positive attitude and willingness (and their family) to participate in this study.

Intervention

Exercise program rationale

The rationale of the iBoneFIT exercise program was described following the Consensus on Exercise Reporting Template (CERT) criteria recommendations [3]. The items detailing the recommendations are shown in **Table 1**.

Since plyometric jump training has been shown to be effective in improving bone health and to maintain the benefits after the intervention in children and adolescents [4], jumping exercise was the basis for the specific exercise type in iBoneFIT. Notwithstanding, the Exercise Guidelines for Cancer Survivors recommend an extended phase of resistance training before progressing to impact loading [5]. In this sense, a recent systematic review highlighted that resistance training should be incorporated at an early age and prior to plyometric training in order to establish an adequate foundation of strength for power training activities [6]. Therefore, all participants started with a familiarization phase aimed to improve muscular fitness before implementing mechanical loading through jumps (Item 7a and 15).

Although the duration of the jumping interventions to be effective on bone outcomes in children and adolescents is unclear, the length of the exercise program was 9 months based on results from previous studies [7,8]. In addition, we considered the fact that bone remodeling process requires approximately 5 months [9]. Dietary counselling on calcium and vitamin D was provided to the participants in both control and intervention groups due to having an adequate calcium and vitamin D levels is important as both interact with physical activity to enhance bone mass (Item 9) [10,11].

Table 1. CERT checklist from iBoneFIT study exercise programme.

Item	Checklist item	Identification (section)
1	Detailed description of exercise equipment	Exercise programme characteristics
2	Detailed description of the qualifications, expertise and/or training	Exercise programme characteristics
3	Describe whether exercises are performed individually or in a group	Exercise programme characteristics
4	Describe whether exercises are supervised or unsupervised; how they are delivered	Exercise programme characteristics
5	Detailed description of how adherence to exercise is measured and reported	Participant adherence and compliance
6	Detailed description of motivation strategies	Exercise programme characteristics
7a	Detailed description of the description rule(s) determining exercise progression	Exercise programme rationale
7b	Detailed description of how the exercise programme was progressed	Periodisation
8	Detailed description of each exercise to enable replication	Session structure
9	Detailed description of any home programme component	Exercise programme rationale
10	Describe whether there are any non-exercise components	Control group
11	Describe the type and number of adverse events that occur during exercise	Exercise programme characteristics
12	Describe the setting in which the exercises are performed	Exercise programme characteristics
13	Detailed description of the exercise intervention	Intervention
14a	Describe whether the exercises are generic (one size fits all) or tailored	Exercise programme characteristics
14b	Detailed description of how exercises are tailored to the individual	Exercise programme characteristics
15	Describe the decision rule for determining the starting level	Exercise programme rationale
16a	Describe how adherence or fidelity is assessed/measured	Participant adherence and compliance
16b	Describe the extent to which intervention was delivered as planned	Participant adherence and compliance

Exercise program characteristics

This home-based intervention was delivered online by making use of social media (Item 4 and 12). Using popular existing social network sites could address issues of reach, engagement, and retention [12,13]. WhatsApp (WhatsApp Inc., Mountain View, CA, USA) is a highly used app in Spain for social networking and that allowed us to send text messages and other types of media (i.e., photos and videos) to the parents of participants. Although WhatsApp was revealed as a feasible method to deliver exercise interventions, Muntaner-Mas et al. [14] suggested that the implementation of behavior change techniques could increment the effectiveness on the outcomes assessed. Thus, five behavior change techniques (i.e., action planning and goal setting, providing instructions and demonstrations of how to perform the behavior, self-monitoring of behavior, providing feedback on performance and information

about health consequences) and a gamification design (i.e., points and rankings) were included to improve the interest and incentive of this non-game program (**Table 2**) (Item 6). These motivational approaches were chosen because of their known effect on physical fitness [14], physical activity [15] and satisfaction [16]. Moreover, parents were told to encourage their children to perform the exercise program in order to increase motivation.

Table 2. Translation and operationalization of BCTs targeting behaviour determinants into BIT elements.

Determinant	BCT	Operationalization	BIT element	Workflow
Perceived behavioural control; Autonomy; Planning; knowledge/awareness	Action planning and goal setting (behaviour)	Inform the participants about the phase of the intervention and goals	WhatsApp group message	Every 2 weeks (Sunday)
Perceived behavioural control; Intentions; Competence; Knowledge/awareness	Provide instructions and demonstrations on how to perform the behaviour	Give instructions and demonstrations about how to perform the training session	Videos with exercise proposals	Every 2 weeks (Sunday)
Perceived behavioural control; Autonomy; Competence; Knowledge/awareness	Prompt self-monitoring of behaviour	Ask the participants to report the intervention compliance	WhatsApp group message	Every 2 weeks (Sunday)
Perceived behavioural control; Relatedness; Competence; Knoledge/awareness	Provide feedback on performance	Inform the participants about their performance in the main exercises (i.e., body mass-based squat, squat jump and countermovement jump)	WhatsApp group message or video	Every 2 weeks (Friday)
Perceived behavioural control; Attitude (beliefs); Knowledge/ awareness	Information about health consequences	Present press releases to emphasize the importance of calcium and vitamin D for bone health	WhatsApp group message	At the beginning of the intervention (Sunday)

BCT behaviour change technique, *BIT* behaviour intervention technology.

A personal trainer with a BSc degree in Sport Sciences developed all the sessions of this program (Item 2, 14a and 14b). The personal trainer recorded 18 exercise sessions and they were uploaded in a private channel of the YouTube website. Each of them was repeated over a 2-week period. The YouTube platform was reported to be an educational tool for health-care conditions among people coping with illness [17]. Every new session for the following 2 weeks was shared through the WhatsApp group every 2 weeks. Finally, participants performed the exercise program individually or accompanied (i.e., with parents or friends) according to their preferences (Item 3) [18]. They were required to record videos and sent through the WhatsApp group in order to supervise the execution of the jumping exercises by the personal trainer. The exercise program was performed on a hard surface (Item 1) [19], and participants were asked to report any pain or injuries at each stage of the intervention (Item 11).

Frequency and volume

Following the updated physical activity guidelines, children and adolescents should include bone-strengthening exercises as part of the daily physical activity on at least 3 days per week. Participants in the iBoneFIT study performed the exercise program three to 4 days per week (preferably on Mondays, Wednesdays and Fridays; or Mondays, Tuesdays, Thursdays and Fridays). If one training session was missed, the participant was able to do it on a different day of the week, provided a minimum of 24 h of rest.

The total volume was 7296 squat/jumps (2000 squats + 5296 jumps). The doses were composed of 136 sessions (10-20 min/session) over 36 weeks. A full description of the training volume and its progression is shown in **Table 3**. In a recent 9-month RCT based on jumping activities with similar dosage we reached 70% of compliance (6216 jumps), and this was enough to improve bone outcomes in non-weight-bearing sport athletes [(7)]. Thus, the proposed volume of 7296 squat/ jumps was likely to elicit the same effect in paediatric cancer survivors.

Table 3. iBoneFIT study exercise programme periodization.

Phase	Warm up[a]	Exercise[b]	Level	Repetitions	Sets a day (Rest[c])	Sessions a Week	Squats/Jumps a Week
1	RAMP	BM-based Squat	1 (1-4 wk)	15	3	4	180
			2 (5-8 wk)	20	4	4	320
Total phase 1 (8 wk)							2000
2	RAMP	SJ	1 (9-12 wk)	10	3	3	90
			2 (13-16 wk)	15	3	4	180
			3 (17-20 wk)	20	4	4	320
Total phase 2 (12 wk)							2360
3	RAMP	CMJ	1 (21-24 wk)	10	3	3	90
			2 (25-28 wk)	12	3	4	144
			3 (29-32 wk)	15	3	4	180
			4 (33-36 wk)	20	4	4	320
Total phase 3 (16 wk)							2936
Total intervention (36 wk)							7296

RAMP raise, activate, mobilise and potentiate, *BM* body mass, *SJ* squat jump, *CMJ* countermovement jump, *WK* week.
[a]Warm up will be focused on dynamic exercises with progressive intensity enhancing optimal core body temperature, motor unit excitability, kinesthetic awareness and ranges of motion.
[b]Each exercise will be suggested to be performed at the pace of the personal trainer managing the session. If not, a self-paced performance will be recommend.
[c]Phase 1 rest = 45 s.
Phases 2 and 3 rest = 1 min.

Periodization

Although Peitz et al. [20] did not find differences between normal, linear and undulating periodisations in youth, iBoneFIT implemented a linear model based on the fact that variation in volume and/or impact loading within the program phases could stimulate greater bone adaptions and reduce boredom and risk of overtraining [5]. The exercise program was divided

in three phases of different durations and impact loadings (i.e., height reached in the different jumps). Each phase was composed of levels with progressive increase in volume (i.e., repetitions, sets per day and sessions per week) as shown in **Table 3**.

The phase 1 corresponded to the first 8 weeks of the exercise program. Participants performed body mass-based squats and the volume increased progressively by modifying the number of repetitions and sets per day. Paediatric cancer survivors could present reduced aBMD and muscular fitness [21], therefore jumping exercise prescription could not be safe. In this sense, body mass-based squat was chosen in this phase following previous studies that observed positive effects on muscular fitness after an 8-week intervention [22,23].

The phase 2 lasted 12 weeks and participants performed squat jumps. In this phase, the volume increased progressively by modifying the number of repetitions, sets per day and sessions per week. Squat jump was chosen as intermediary exercise before the use of countermovement jump since the jump height reached is lower and hence, ground reaction forces produced at the landing are lower [24]. Furthermore, squat jump training reduces the degree of muscle slack on the push-off phase [25] which could supply a better execution of the countermovement jump afterwards.

The phase 3 was the longest phase of the exercise program with 16 weeks. Participants performed countermovement jumps and the volume of this phase increased progressively by modifying the number of repetitions, sets per day and sessions per week. Countermovement jump was chosen in this phase since it produces a huge force application (~400 times body mass/second) and ground reaction forces (~5 times body mass) in youth [26,27]. Countermovement jump has been previously reported to be valid and reliable in children [28].

Session structure

The structure of the exercise sessions was: 1) warm up; 2) squat/jumps training; 3) cool down. Briefly, the warm up was based on RAMP methodology (i.e., raise, activate, mobilize and potentiate) in order to maximize middle-term performance of the main exercises (i.e., squat/jumps exercises) [29]. Eight exercises focused on the brace, squat, lunge or jump patterns were included in this part of the session. Squat/jumps training comprised body mass-based squats, squat jumps and countermovement jumps in phase 1, phase 2 and phase 3, respectively. Finally, participants performed a cool down including static stretching and relaxing exercises (Item 8).

Control group

Participants randomly allocated to the CG received information on the recommendations of calcium and vitamin D [30]. Educational leaflets and infographics based on the current recommendations [30] were delivered to the participants at the beginning of the study (Item 10). After finishing the study, they were offered the same online exercise program.

Outcomes

The primary outcome of our study was bone health. The secondary outcomes included anthropometric measurements, body composition, physical fitness components, free-living physical activity, blood samples, calcium and vitamin D intake, health-related quality of life and mental health. Assessments were conducted at baseline, repeated at post-test (i.e., after 2 weeks of intervention or control condition at most). Participants were assessed for the post-test following the order through which they were tested at baseline, to avoid cofounding by time between baseline and the other assessments.

Data obtained on the assessments were recorded on a paper print-out and entered into an Excel file for statistical analysis. Questionnaires were filled using Google Forms which allowed us to record the data without hand-written management. In compliance with the Personal Information Protection Act, the names of all participants were not disclosed, and an identifier number was used for each participant. All participants were informed that the clinical data obtained in the trial would be stored in a computer and would be handled with confidentiality.

Primary outcome: bone health

Dual-energy X-ray Absorptiometry (DXA)

A DXA (Hologic Series Discovery QDR, Bedford, MA, USA) was used throughout the study to obtain BMC (g) and aBMD (g/cm^2) for the hip, lumbar spine and total body less head. Furthermore, lean soft tissue mass (g), fat mass (kg) and body fat percentage (%) for the whole body were obtained from total body scans. APEX software (version 4.0.2) was used to analyze the scans following the recommendations for children and adolescents [31]. Equipment calibration, participant setting, and scan analyses were performed by the same researcher. DXA uses a minimal radiation (i.e., spending a day outside in the sunshine) and the effective dose for the scans in children has been set in 3-6 μSv [32].

Hip Structural Analysis (HSA)

HSA is a DXA-based software that analyses hip scans to estimate bone geometric properties of the proximal femur. This software analyses structural characteristics through the distribution

of bone mineral mass in a line of pixels across the bone axis [33]. These geometric estimates in the proximal femur were derived from: 1) the cross-sectional area (mm^2); 2) section modulus (mm^3); and 3) the cross-sectional moment of inertia (mm^4). For these variables, the short-term coefficient of variation has been reported to be between 2.4 and 10.1% [34].

Trabecular Bone Score (TBS)

TBS is a DXA-based software (iNsight version 3.0, Medimaps, Pessac, France) that indirectly assesses the state of trabecular microarchitecture in the lumbar spine. Based on experimental variograms of the projected DXA image, TBS evaluates the heterogeneity of the grey-levels pixels of the aBMD and higher heterogeneity implies worse trabecular connectivity [35]. Low values reported in this parameter have been associated with a higher fracture risk, and therefore it is considered an index of bone quality [36]. The short-term coefficient of variation for TBS has been reported to be between 1.7 and 2.1% for spine aBMD in 92 individuals with repeated spine DXA scans performed within 28 days [37].

3D-DXA Modelling

3D-SHAPER is a DXA-based software (version 2.2, Galgo Medical, Barcelona, Spain) that derives 3D analyses from the hip DXA scans. Details of the model algorithm are published elsewhere [38]. Briefly, this software uses a 3D statistical shape and density of the proximal femur built from a database of quantitative computed tomography (QCT) scans of Caucasian population [38]. The 3D-SHAPER assessed bone parameters such as the cortex, the femoral shape and the trabecular macrostructure [39]. The cortex is segmented by fitting a mathematical function of the cortical thickness (mm), cortical volumetric BMD (cortical vBMD, mg/cm^3), the location of the cortex, the density of surrounding tissues and the imaging blur to the density profile computed along the normal vector at each node of the proximal femur surface mesh [39]. In addition, the cortical surface BMD (cortical sBMD, mg/ cm^2) is computed at each vertex of the femoral surface mesh, as the multiplication of the cortical thickness (cm) by the cortical vBMD along its thickness [40]. Any increase in either cortical thickness or cortical vBMD would ensure an increase in cortical sBMD. Nevertheless, if cortical thickness and cortical vBMD vary in opposite ways, cortical sBMD would remain unchanged. All measurements were computed over the total femur (i.e., the shaft, the intertrochanteric and the union of the neck) according to the trabecular, cortical and integral compartments. Correlation coefficients between BMD computed by 3D-SHAPER and QCT of the total femur have been reported to be 0.86–0.95, whereas the correlation coefficients of BMD computed by 3D-SHAPER with

BMD computed by QCT have been reported to be 0.91 [38]. The short-term coefficients of variations of aBMD measurements have been reported to be 1.5, 4.5, 1.7 and 1.5% for cortical thickness, trabecular vBMD, cortical vBMD and cortical sBMD, respectively [40].

Secondary outcomes

Anthropometric measurement, body composition and somatic maturation

Body mass (kg) was measured with an electronic scale (SECA 861, Hamburg, Germany) with an accuracy of 100 g. Height (cm) was measured by using a precision stadiometer (SECA 225, Hamburg, Germany) to the nearest 0.1 cm. Body mass index (BMI) was calculated as body mass (kg)/height (m^2), and the participants were classified into BMI categories according to sex- and age-specific cut offs [41].

In addition to DXA measurements, a bioimpedance scale (Tanita BC-418 MA; Amsterdam, The Netherlands; range: 2-200 kg; precision: 0.1 kg; body fat percentage increments: 0.1%) estimated the percentage of body fat of the participants. The assessment was carried out in fasting state according to the manufacturer's instructions. Despite the measured error, bioelectrical impedance analysis was used to assess body fat as it is considered a practical method in addition to DXA [42]. Somatic maturation was assessed using the prediction of years from PHV using validated algorithms for children [43].

Physical fitness

The ALPHA fitness test battery was used to assess physical fitness. These field-based fitness tests have been shown to be valid, reliable and related to health in children and adolescents [44]. In brief, muscular fitness was assessed with the handgrip strength and standing long jump tests. Both tests were performed twice, and the best score was retained.

Perceived physical fitness was assessed by the International Fitness Scale (IFIS). The IFIS is a short, simple and self-administered scale that has been validated in children and adolescents [45,46]. This 5-item scale asks the participants about their physical fitness comparing with their colleagues.

Physical activity and sedentarism

Physical activity and SB were objectively assessed at the baseline, post-intervention and follow-up measurements. Participants worn a tri-axial accelerometer (ActiGraph GT3X, Pensacola, FL, USA) attached to the non-dominant wrist over seven consecutive days (24 h/day) and they would remove it only for water-based activities (i.e., bathing or swimming).

They also had a diary in order to record the time when they went to bed, woke up and removed the device. Correlation coefficient between accelerometer measured metabolic energy equivalents and indirect calorimetry has been reported to be 0.65 [47], whilst correlation coefficient of accelerometer impact loading and ground reaction forces by force platforms has been reported to be 0.74 [48].

In addition, information on self-reported physical activity and SB were obtained by the cross-translated and adapted version of the Youth Activity Profile (YAP) questionnaire (available at: https://profith.ugr.es/yap?lang=en). The YAP questionnaire was developed at the Iowa State University and validated in children [49]. This self-administered 7-day recall questionnaire collects data from items regarding physical activity in the school setting, physical activity out of the school setting, activity immediately after school, activity during the evening and activity during each weekend day. Moreover, the bone-specific physical activity questionnaire (BPAQ) was used to assess the influence of historical physical activity (i.e., activities in which you have ever participated, and activities practiced in the last 12 months) on skeletal health. It has been reported that BPAQ is a valid instrument to account for the effects of previous physical activities on the skeleton [27].

Calcium intake and vitamin D status

To correctly interpret bone health of the participants, an assessment of dietary intake of calcium was completed at the baseline, post-intervention and follow-up measurements. A validated food-frequency questionnaire was used to estimate calcium intake [50]. In addition to plasma 25-hydroxyvitamin D levels obtained from blood analyses, a vitamin D questionnaire to assess the status of this prohormone was implemented [51].

Blood samples

Fasting blood samples were collected by venepuncture between 8:00 and 10:00 after an overnight fast. The methodology for shipment, preparation and collection of the blood samples was standardized among all participating hospitals. A set of parameters obtained from hematological and biochemical analyses were available from the hospitals as part of the follow-up protocols.

Health-related quality of life and mental health

The Paediatric Quality of Life Inventory (PedsQLTM 4.0 Generic Core Scales) was used to assess quality of life. PedsQLTM is validated in paediatric cancer survivors and has been

successfully used [52]. This 23-item scale assesses quality of life considering five domains of health (i.e., physical functioning, emotional functioning, psychosocial functioning, social functioning and school functioning). Results from our participants in all domains of PedsQLTM were compared to published normative data [53].

Childhood anxiety was assessed with the State-Trait Anxiety Inventory for Children (STAIC-T). This inventory has been extensively validated in Spanish children [54]. Depression was measured with the Children Depression Inventory (CDI), which consists of 27 items that assesses 5 domains (interpersonal problems, ineffectiveness, negative mood, anhedonia and negative self-esteem) [55]. Rosenberg Self-Esteem scale was used to assess self-esteem and has been validated with children and adolescents [56]. We used the Positive Affect Schedule for children (PANAS-C) in order to measure both positive and negative affect [57]. The original PANAS-C reported appropriate values of internal consistency (0.86 for the positive affect and 0.82 for the negative affect). Happiness was assessed by the Subjective Happiness Scale (SHS) whose Spanish version has shown appropriate test-retest reliability, internal consistency and convergent validity [58]. Dispositional optimism was assessed with the Life Orientation Test-Revised (LOT-R) [59]. LOT-R is an instrument with good internal consistency (0.71 for the total score and of 0.64 and 0.77 for the optimism and pessimism, respectively) [60].

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RESULTS AND DISCUSSION

Chapter 4. Effect of exercise on bone health in children and adolescents with cancer during and after oncological treatment: A systematic review and meta-analysis

Abstract

Background. Although regular physical activity and exercise program might improve bone health caused by oncological treatment and the disease itself, it remains unknown the pooled effect of exercise interventions following frequency, intensity, time and type prescriptions.

Objective. This systematic review and meta-analysis aimed to synthesise evidence regarding the effectiveness of exercise interventions on bone health in children and adolescents with cancer during and after oncological treatment.

Methods. A systematic search was conducted in the MEDLINE (via PubMed), Web of Science and Scopus databases from November 2021 to January 2022. RCTs and non-RCTs reporting pre-post changes of the effectiveness of exercise interventions on DXA-measured bone parameters in young population (1-19 years) during or after oncological treatment were included. Pooled ESs and 95%CIs were calculated. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.

Results. A total of eight trials with 341 participants were included. The meta-analyses did not reveal a statistically significant increase in whole body aBMD (ES=0.10; 95%CI: -0.14, 0.34), lumbar spine (ES=0.03; 95%CI: -0.21, 0.26) or femoral neck (ES=0.10; 95%CI: -0.37, 0.56). Similarly, during the oncological treatment phase the ES was 0.04 (95%CI: -0.17, 0.25) and after the ES was 0.07 (95% CI: -0.20, 0.33).

Conclusion. In comparison to standard care, exercise interventions were inappropriate and therefore, ineffective to illustrate any beneficial effect on bone health in children and adolescents with cancer during and after oncological treatment.

Systematic Review Registration: PROPERO registration number: CRD42022310876.

Introduction

Paediatric cancer survival has experienced an unparalleled increase because of the advances in cancer detection and treatment [1]. The current overall 5-year survival rate has risen up to 85% in children and adolescents [2,3]. However, all oncological treatments and the disease itself can decrease bone mass through endocrine alterations, such as gonadal dysfunction, growth hormone deficiency, and altered body composition [4]. This is shown by a decreased bone formation and increased bone resorption in cancer-treated children [5]. Research has shown that between 20% and 50% of paediatric cancer patients present impaired bone mass [4,6]. Moreover, paediatric cancer occurs during a critical phase for bone development and bone strengthening, since up to 95% of the adult bone mass may be accrued by the end of adolescence [7-9]. Therefore, implementing feasible strategies to counteract cancer-related bone loss due to cancer during growth are vital to optimize skeletal health during growth and reduce the risk of osteoporosis later in life.

Although acquiring the peak bone mass strongly depends on genetics [10,11] regular physical activity and exercise program may contribute to achieve it [12]. Evidence has shown that exercise is safe during and after paediatric oncological treatment, even during the most aggressive phases (i.e., hematopoietic stem cell transplantation) [13,14] and hence, it might contribute to preserve bone health in paediatric cancer patients during and after oncological treatment [4,15]. Weight-bearing impact exercise of high intensity including strains in different axes and multiple rest periods is known to improve bone mass [16,17]. Interestingly, a systematic review showed that plyometric jump training causes improvements in aBMD, BMC and structural properties in healthy children and adolescents [18]. In adolescent males, a jump-based intervention enhanced bone parameters in those engaged in non-osteogenic sports and with poorer bone health [19,20]. However, there is limited evidence of the effects of exercise on bone parameters in paediatric cancer patients, the reported findings are inconsistent [21,22] and some of the studies have been carried out in a very small sample of participants [23,24]. The interest in exercise oncology has sharply risen during the last decade and therefore, there is a need to know the pooled effect of exercise interventions on bone health in young paediatric cancer patients.

Therefore, the aims of this systematic review and meta-analysis were to (1) determine the pooled effect of exercise interventions from RCTs and non-RCTs in children and adolescents with cancer during and after oncological treatment on bone health and (2) explore factors influencing the response of the exercise intervention. We hypothesized that (1) exercise would have a positive effect on bone health in this population when compared with control non-

exercise groups, and (2) enhancements will be greater in studies with longer interventions that involve weight-bearing and impact exercises of high intensity.

Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Table S1**) [25,26].

Search strategy

This systematic review and meta-analysis were registered in the International Prospective Register for Systematic Reviews (PROSPERO; registration number CRD42022310876). The recommendations of the Cochrane Collaboration Handbook for conducting systematic reviews and meta-analyses were strictly followed [27]. A systematic search of the literature was conducted in various electronic databases: MEDLINE (via PubMed), Web of Science and Scopus databases from November 2021 to January 2022. Intervention studies addressing the change in aBMD and BMC after exercise program in paediatric cancer participants in the childhood and adolescence periods were eligible. This systematic search was only restricted by language, solely including those studies published in English. We also manually screened other sources for additional records (i.e., references from previous reviews) and contacted authors for missing information when necessary. No studies were included from manual screenings. Combinations of the following keywords were used in the search (**Table S2**): exercis*, move*, moving, sport*, train*, "physical activity", weightbear*, "high impact", running, walk*, strength*, "physical fitness", step*, gymnastic, balance, bone, cancer, onco*, myelo*, leukaemia, leukemia, neoplasm*, lympho*, carcinoma, tumor, tumour, sarcoma, child*, adolescen*, young*, boy*, girl*, pediatric*, paediatric*, trial*, random, intervention*, program* and rehabilitation. The literature search was complemented by reviewing references of the articles considered eligible.

Study selection

Study inclusion criteria were as follows: (1) participants: paediatric cancer population (aged 1-19 years) during and after oncological treatment irrespective of the type of the treatment at any time point; (2) study design: intervention studies based on exercise program (RCT and non-RCTs) with a non-exercising control group; (3) exposure: exercise program with a minimum of one month of duration without restrictions on the setting, resistance, aerobic, walking, gymnastic, yoga, whole-body vibration and balance interventions were included, no minimal

adherence required and the concomitant exposure to other treatment such as nutritional supplementation with calcium or vitamin D to both groups was allowed; and (4) outcome: aBMD and BMC assessed using DXA. Exclusion criteria were as follows: (1) studies including individuals older than 19 years old; (2) non-eligible publication types, such as review articles, editorials, comments, guidelines or case reports; (3) assessment of aBMD and BMC using other methods (i.e., computed tomography); and (4) studies published in any language other than English. Based on the selection criteria, all studies were independently screened for inclusion by two reviewers and disagreements were solved by consensus or involving a third researcher. A total of 932 potential manuscripts were identified following database examination (**Figure 1**), eight of them met the inclusion criteria and were, therefore, included in the meta-analysis.

Data extraction and risk of bias assessment

All articles retrieved from the respective databases were exported and handled in an EndNote library (Endnote version X7). After removing the duplicated articles, two researchers independently read the titles and abstracts to screened out the irrelevant articles according to the inclusion/exclusion criteria, and finally screened the articles by reading the full text. Any conflicts were solved by consensus with a third researcher.

The following data were retrieved from the original reports: (1) first author and year of publication; (2) country from which the data were collected; (3) study design; (4) sample characteristics (age, sample size, body mass index, height, weight, and type of cancer); and (5) the method used for measuring bone measurement characteristics (aBMD, volumetric BMD, bone mineral apparent density and BMC, including values for whole body, lumbar spine, and femoral neck) at baseline and at end of follow-up. Besides, data concerning exercise program were extracted from the original manuscripts: (1) frequency, (2) intensity, (3) time, (4) type, (5) volume, (6) progression, (7) intervention duration, (8) attendance, (9) supervision, (10) home exercise program, (11) control group and (12) other characteristics.

Two researchers independently assessed the risk of bias and any discrepancies were resolved by a third reviewer. The Cochrane Collaboration's tool for assessing the risk of bias (RoB2.0) was used to assess the certainty of the evidence of the RCT studies [28]. This tool covers bias in five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. According to this assessment tool, the studies were rated as 'low risk of bias' (if all domains were judged as 'low risk'), 'some concerns' (if there was at least one domain rated as having 'some concerns'), or 'high risk of bias' (if there was at least one domain judged as 'high risk').

The Joanna Briggs Institute Critical Appraisal Tool [29] for Quasi-Experimental Studies were used to assess the certainty of the evidence of the non-randomized experimental studies. According to this assessment tool, the studies were rated as good (i.e., most criteria met, with a low risk of bias), fair (i.e., some criteria met, with a moderate risk of bias), or poor (i.e, few criteria met, with a high risk of bias). No studies were excluded based on the quality appraisal.

Statistical considerations

The inverse-variance-weighted method used to compute the pooled ES estimate and the 132 respective 95%CI. An ES was calculated for the pre-post aBMD mean values or the mean value change using Sn's d index. ES values of 0.2 were considered a weak effect, values of 0.5 were considered a moderate effect, values of 0.8 were considered a strong effect, and values larger than 1.0 were considered a very strong effect. When studies reported means and standard errors (SE) or 95% CI we used the formulas, SD = sqrt (sample size) * SE and SD = sqrt (sample size) * [(upper limit 95% CI - lower limit 95% CI)/3.92], to convert to SD. Additionally, when studies reported pre-post aBMD mean values or the mean value change data in graphs, the online tool WebPlotDigitizer (https://apps.automeris.io/wpd/) was used to extract the data for the ES calculation.

Heterogeneity of results across studies was assessed using the I^2 statistic [30]. I^2 values were considered as follows: might not be important (0%-40%), may represent moderate heterogeneity (30%-60%), may represent substantial heterogeneity (50%-90%), or considerable heterogeneity (75%-100%); the corresponding P values also were considered. Finally, we calculated the statistic $\tau 2$ to establish the size and clinical relevance of heterogeneity. A $\tau 2$ estimate of 0.04 can be considered as low, 0.14 as moderate, and 0.40 as a substantial degree of the clinical relevance of heterogeneity [31].

Exploratory subgroups analyses were conducted according to the type of aBMD region (whole body, lumbar spine or femoral neck) and patient status (during oncological treatment or surviving patients). Furthermore, sensitivity analyses (systematic reanalysis while removing studies one at a time) and subgroup analyses were conducted to assess the robustness of the summary estimates. The results of the sensitivity analyses were considered meaningful when the resulting estimates were modified beyond the CIs of the original summary estimate. In addition, sensitivity analyses provided insight into whether any study or special condition included in the studies accounted for a large proportion of the heterogeneity among the ES pooled estimations, based on the change in I^2 values (and associated categories previously reported).

Finally, small-study effects and publication bias were examined using the Doi plot and the Luis Furuya–Kanamori index (LFK index). No asymmetry, minor asymmetry or major asymmetry were considered with values of one, between one and two, and two, respectively [32]. Statistical analyses were performed using STATA SE software, version 14 (StataCorp, College Station, Texas).

Results

The PRISMA flow diagram for the systematic search and study selection is shown in **Figure 1**.

Level of evidence and risk of bias of the studies

The overall risk of bias for RCTs showed two studies with low risk (40%) and three studies with some concerns (60%) (**Table S3**). Regarding the specific domains, in the randomization process, missing outcome data, and measurement of outcome domains, all the studies (n=5, 100%) were scored as low risk. In the deviations from intentional interventions and selection of the reported results domains, two studies (40%) were scored as some concerns and three studies as low risk (60%).

The risk of bias for non-randomized experimental studies showed two studies with high quality (66,67%) and one study with medium quality (33,33%). When the studies were analyzed by individual domains, all the studies (n=3, 100%) made clear what the 'cause' was and what the 'effect' was, had a control group, had multiple measurements of the outcome both pre and post the intervention/exposure, adequately described and analyzed any differences between groups in terms of their follow up, and measured in the same way the outcomes of included participants and in a reliable way. In addition, two studies included similar participants (66.67%), and one study (33.3%) included participants in any comparisons receiving similar treatment/care other than the exposure or intervention of interest, and used an appropriate statistical analysis (**Table S4**).

Characteristics of the participants and assessment methods selected

Table 1 shows the participants characteristics of the eight studies included in this meta-analysis. Participants age ranged from 1.3 to 18 years old, with sample sizes ranging from 21 to 75 participants (mean = 48 participants, total = 341). The type of cancer included acute lymphoblastic leukemia, acute myeloid leukemia, Hodgkin lymphoma or non-Hodgkin lymphoma, chronic myeloid leukemia or Burkitt, central nervous system/brain tumor, solid

tumor, neuroblastoma, Wiskott–Aldrich syndrome or osteosarcomas and Ewing sarcoma. Concerning the assessment methods carried out in the studies, five studies used the Lunar Prodigy, one study used the Hologic, one study used both the Lunar Prodigy or the Hologic and one study used both the Hologic and Lunar Prodigy.

Characteristics of the studies selected

These eight studies reported aBMD and BMC changes after exercise interventions in paediatric cancer survivors during (n=4) and after (n=4) oncological treatment (**Table 1**) [21-24,33-36], compared with a non-exercising control group. They were published between 2009 and 2021 and were carried out in six different countries: two studies conducted in The Netherlands, two in Saudi Arabia, one in USA, one in USA and Canada, one in Israel and one in Germany.

There were five RCTs [21,22,34-36], and 3 non-RCTs [23,24,33]. **Table 2** shows the eight screened studies highlighting their FITT interventions. The characteristics of the interventions are as follows: (1) Frequency, ranged from 1.5 to seven days a week (mean = three days a week); (2) Intensity, was differently reported depending on the type of exercise in terms of heart rate peak (HRpeak), mechanical stimulation from a platform, Borg's scale, weight-bearing, light-to-moderate, moderate-to-vigorous and high intensity, while two studies did no describe the intensity target; (3) Time per session, ranged from 10 to 60 minutes (mean = 36 minutes) but one study did not report it and time per intervention, ranged from three to 30 months (mean = 13 months); and (4) Type, four studies conducted a concurrent exercise intervention (resistance and endurance training), three studies implemented a resistance training intervention and one study carried out a low-magnitude, high-frequency mechanical stimulation. Control groups did not receive an exercising treatment.

Meta-analysis

The eight studies reporting aBMD changes after exercise interventions in paediatric cancer survivors during (n=4) and after (n=4) oncological treatment were included in this meta-analysis with a total of 341 participants. The pooled ES of exercise interventions showed no evidence of an effect on aBMD (ES = 0.05; 95%CI: -0.11, 0.22) with not important heterogeneity (I^2 = 0.0%, p = 0.961; $\tau 2$ = 0.000) (**Figure 2**).

Exploratory subgroup analyses by aBMD region showed an ES of: i) 0.10 (95%CI: -0.14, 0.34) with not important heterogeneity (I^2 = 0.0%, p = 0.427; τ^2 = 0.000) for whole body, ii) 0.03 (95%CI: -0.21, 0.26) with not important heterogeneity (I^2 = 0.0%, p = 0.967; $\tau 2$ = 0.000)

for lumbar spine and, iii) 0.10 (95%CI: -0.37, 0.56) with no evidence of important heterogeneity (I^2 = 0.0%, p = 0.896; $\tau 2$ = 0.000) for femoral neck (**Figure 3**).
Additionally, during the treatment phase the ES was: i) 0.04 (95%CI: -0.17, 0.25) with not important heterogeneity (I^2 = 0.0%, p = 0.701; $\tau 2$ = 0.000) and after the treatment phase, ii) 0.07 (95%CI: -0.20, 0.33) with not important heterogeneity (I^2 = 0.0%, p = 0.909; $\tau 2$ = 0.000) (**Figure 4**).

The pooled ES estimate for exercise interventions was not modified in aBMD when studies were removed from the analysis one at a time to examine the impact of individual studies. There was a minor asymmetry of small-study effects for exercise interventions, as evidenced by visual inspection of the Doi plot and LFK index (1.56) (**Figure 5**).

Table 1. Descriptive characteristics of included studies.

			Population characteristics at baseline								Outcomes	
Reference	Country	Design	Age, years	Sample size [n (% male)]	BMI, kg/m^2	Height, cm/m	Weight, kg	Cancer-type	Treatment phase /Type	Method	Baseline Bone	Follow-up
Hartman et al., 2009 (22)	The Netherlands	Prospective randomized study	Exercise group: Mean (range) 5.3 (1.3-15.6) Control group: Mean (range) 6.2 (1.7-17.1)	Exercise group: 20 (56%) Control group: 21 (62%)	Exercise group: SDS -0.33 Control group: SDS -0.38	Exercise group: SDS -0.11 Control group: SDS -0.10	Exercise group: SDS -0.40 Control group: SDS -0.09	Exercise group: 25 Acute lymphoblastic leukemia Control group: 26 Acute lymphoblastic leukemia	During treatment/ Chemotherapy	X-ray absorptiometry (DXA; Lunar DPX-L, Madison, WI)	Exercise group: SDS WB aBMD (g/cm^2): -0.10 LS aBMD (g/cm^2): -0.42 LS BMAD (g/cm^2): 0.14 Control group: SDS WB aBMD (g/cm^2): -0.18 LS aBMD (g/cm^2): -0.96 LS BMAD (g/cm^2): -0.48	Exercise group: SDS WB ΔaBMD (g/cm^2): 0.42 LS ΔaBMD (g/cm^2): 0.10 LS ΔBMAD (g/cm^2): 0.12 Control group: SDS WB ΔaBMD (g/cm^2): 0.35 LS ΔaBMD (g/cm^2): 0.14 LS ΔBMAD (g/cm^2): -0.04
Muller et al., 2014 (23)	Germany	Non-randomized interventional study	Exercise group: Mean ± SD 15.2 ± 2.0 Control group: Mean ± SD 12.2 ± 2.6	Exercise group: 10 (40%) Control group: 11 (45%)	Exercise group: Mean ± SD 19.9 ± 2.9 Control group: Mean ± SD 18.2 ± 3.9	Exercise group: Mean ± SD 1.71 ± 0.10 Control group: Mean ± SD 1.54 ± 0.08	Exercise group: Mean ± SD 57.9 ± 7.2 Control group: Mean ± SD 44.0 ± 12.6	Exercise group: 7 osteosarcomas and 3 Ewing sarcoma Control group: 7 osteosarcomas and 4 Ewing sarcoma	During treatment/ Surgery and/or radiotherapy	X-ray absorptiometry (DXA), Lunar Prodigy system (enCore 2006, Software version 10.51.006, GE Healthcare)	Exercise group: Mean (SEM) LS (L2-L4) vBMD (g/cm^3): 0.348, (0.020) LS (L2-L4) aBMD (g/cm^2): 1.074 (0.054) LS (L2-L4) BMC (g): 42.06 (2.58) FN vBMD (g/cm^3): 0.418 (0.024) FN aBMD (g/cm^2): 1.103 (0.043) FN BMC (g): 4.85 (0.27) Control group: Mean (SEM) LS (L2-L4) vBMD (g/cm^3): 0.322 (0.019) LS (L2-L4) aBMD (g/cm^2): 0.961 (0.050) LS (L2-L4) BMC (g): 35.47 (2.43) FN vBMD	Exercise group: Mean (SEM) LS (L2-L4) vBMD (g/cm^3): 0.347, (0.018) LS (L2-L4) aBMD (g/cm^2): 1.068 (0.055) LS (L2-L4) BMC (g): 41.23 (2.76) FN vBMD (g/cm^3): 0.406 (0.027) FN aBMD (g/cm^2): 0.998 (0.052) FN BMC (g): 4.72 (0.30) Control group: Mean (SEM)

											(g/cm^3): 0.381 (0.023) FN aBMD (g/cm^2): 0.898 (0.040) FN BMC (g): 4.06 (0.25)	LS (L2-L4) vBMD (g/cm^3): 0.294 (0.017) LS (L2-L4) aBMD (g/cm^2): 0.875 (0.051) LS (L2-L4) BMC (g): 32.97 (2.60) FN vBMD (g/cm^3): 0.332 (0.027) FN aBMD (g/cm^2): 0.791 (0.052) FN BMC (g): 3.63 (0.30)
Cox et al., 2017 [35]	USA and Canada	RCT	NR	Exercise group: 35 (64.2%) Control group: 40 (66.7%)	NR	NR	NR	Exercise group: 53 Acute lymphoblastic leukemia Control group: 55 Acute lymphoblastic leukemia	During treatment/ Chemotherapy	Dual-energy X-ray absorptiometry (DEXA) using the GE Lunar Prodigy (Atlanta and Toronto) or the Hologic (SJCRH and MDA)	<u>Exercise group:</u> LS (L1-L4): Z-score (SEM) -0.21 (± 1.27) <u>Control group:</u> LS (L1-L4) Z-score: Z-score (SEM) -0.62 (± 1.14)	<u>Exercise group:</u> LS (L1-L4) Z-score: Z-score (SEM) -0.55 (± 0.86) <u>Control group:</u> LS (L1-L4) Z-score: Z-score (SEM) -0.78 (± 1.11)
Waked et al., 2018 [21]	Saudi Arabia	RCT	<u>Exercise group:</u> Mean ± SD 9.26 ± 2.39 <u>Control group:</u> Mean ± SD 9.91 ± 2.09	Exercise group: 23 (65.2%) Control group: 23 (78.3%)	<u>Exercise group:</u> Mean ± SD 18.15 ± 1.79 <u>Control group:</u> Mean ± SD 19.12 ± 1.56	<u>Exercise group:</u> Mean ± SD 124.13 ± 11.95 <u>Control group:</u> Mean ± SD 129.30 ± 10.8	<u>Exercise group:</u> Mean ± SD 28.52 ± 7.39 <u>Control group:</u> Mean ± SD 32.26 ± 6.57	Exercise group: 23 Acute lymphoblastic leukemia Control group: 23 Acute lymphoblastic leukemia	During treatment/ Chemotherapy	Dual Energy X-ray Absorptiometry (DEXA) (DXA, Lunar DPXL/PED, Madison, Wisconsin, U.S.A.).	<u>Exercise group:</u> Mean (SD) WB aBMD (g/cm^2): 0.811 ± 0.072 LS (L2-L4) aBMD (g/cm^2): 0.727 ± 0.059 <u>Control group:</u> Mean (SD) WB aBMD (g/cm^2): 0.814 ± 0.071 LS (L2-L4) aBMD (g/cm^2): 0.712 ± 0.050	<u>Exercise group:</u> Mean (SD) 6 months WB aBMD (g/cm^2): 0.842 ± 0.076 LS (L2-L4) aBMD (g/cm^2): 0.778 ± 0.035 12 months WB aBMD (g/cm^2): 0.869 ± 0.069 LS (L2-L4) aBMD (g/cm^2): 0.808 ± 0.058

Dubnov-Raz et al., 2015 [24]	Israel	Interventional trial	<u>Exercise group:</u> Mean (range) 11.1 (7.8-13.8) <u>Control group:</u> Mean (range) 11.8 (9.0-12.8)	Exercise group: 10 (40 %) Control group: 11 (50 %)	<u>Exercise group:</u> Mean (range) 19.6 (17.6-3.9) <u>Control group:</u> Mean (range) 18.7 (17.1-21.2)	<u>Exercise group:</u> Mean (range) 144 (130-152) <u>Control group:</u> Mean (range) 148 (127-158)	<u>Exercise group:</u> Mean (range) (33.0-52.8) <u>Control group:</u> Mean (range) 40.6 (29.1-54.9)	Exercise group: 5 Acute lymphoblastic leukemia, 1 Burkitt lymphoma, 1 acute myeloid leukemia, 1 acute promyelocytic leukemia, 1 juvenile myelomonocytic leukemia and 1 neuroblastoma Control group: 3 Acute lymphoblastic leukemia, 2 Burkitt lymphoma, 2 Hodgkin lymphoma, 1 medulloblastoma, 1 rhabdomyosarcoma, 1 Wilms' tumor, 1 severe aplastic anemia and 1 Wiskott–Aldrich syndrome	After treatment/ Chemotherapy and/or steroids and/or bone marrow transplantation	Dual energy X-ray absorptiometry with Lunar DPX software version 3.6 (Lunar Prodigy; General Electric Healthcare, Madison, Wisconsin, USA)	<u>Exercise group:</u> Median (IQR) B aBMD (g/cm^2): 0.95 (0.87–1.01) WB BMC: (g): 1435 (1117–2051) LS (L1-L4) aBMD (g/cm^2): 0.84 (0.78–0.92) FN aBMD (g/cm^2): 0.85 (0.75–0.89) <u>Control group:</u> Median (IQR) WB aBMD (g/cm^2): 0.90 (0.87–0.99) WB BMC (g): 1293 (1124–2069) LS (L1-L4) aBMD (g/cm^2): 0.75 (0.63–0.82) FN aBMD (g/cm^2): 0.82 (0.70–0.97)	<u>Control group</u>: Mean (SD) 6 months WB aBMD (g/cm^2): 0.805 ± 0.056 LS (L2-L4) aBMD (g/cm^2): 0.716 ± 0.040 12 months WB aBMD (g/cm^2): 0.797 ± 0.055 LS (L2-L4) aBMD (g/cm^2): 0.724 ± 0.032 <u>Exercise group:</u> Median (IQR) WB aBMD (g/cm^2): 0.97 (0.86–1.03) WB BMC (g): 1631 (1076–1993) LS (L1-L4) aBMD (g/cm^2): 0.88 (0.79–0.97) FN aBMD (g/cm^2): 0.89 (0.82–0.95) <u>Control group</u>: Median (IQR) WB aBMD (g/cm^2): 0.91 (0.90–1.03) WB BMC (g): 1445 (1222–2139) LS (L1-L4) aBMD (g/cm^2): 0.79 (0.69–0.85) FN aBMD (g/cm^2): 0.86 (0.72–0.97)

Braam et al., 2018 [34]	The Netherlands	RCT	<u>Exercise group:</u> Mean ± SD 13.4 ± 3.1 <u>Control group:</u> Mean ± SD 13.1 ± 3.1	Exercise group: 26 (53%) Control group: 33 (55%)	NR	<u>Exercise group:</u> Mean ± SD 158.9 ± 16.5 <u>Control group:</u> Mean ± SD 154.5 ± 17.2	<u>Exercise group:</u> Mean ± SD 51.6 ± 16.0 <u>Control group:</u> Mean ± SD 49.2 ± 16.9	Exercise group: 8 Acute lymphoblastic leukemia, 12 acute myeloid leukemia or Hodgkin lymphoma or non-Hodgkin lymphoma or chronic myeloid leukemia or Burkitt, 1 central nervous system/brain tumor and 9 solid tumors Control group: 12 Acute lymphoblastic leukemia, 13 acute myeloid leukemia or Hodgkin lymphoma or non-Hodgkin lymphoma or chronic myeloid leukemia or Burkitt, 6 centrals nervous system/brain tumor and 7 solid tumors	After treatment/ Chemotherapy and/or radiotherapy	Dual-energy-X-ray absorptiometry (DXA)-scanner. (Hologic DXA scanner with the same software) + Lunar	<u>Exercise group:</u> Mean (SD) LS (L1-L4) aBMD (g/cm^2): 0.78 (± 0.21) <u>Control group:</u> Mean (SD) LS (L1-L4) aBMD (g/cm^2): 0.75 (± 0.18)	<u>Exercise group:</u> Mean (SD) Post Short-term LS (L1-L4) aBMD (g/cm^2): 0.78 (± 0.20) Post Long-term LS (L1-L4) aBMD (g/cm^2): 0.83 (± 0.23) <u>Control group:</u> Mean (SD) Post Short-term LS (L1-L4) aBMD (g/cm^2): 0.76 (± 0.20) Post Long-term LS (L1-L4) aBMD (g/cm^2): 0.78 (± 0.21)
Mogil et al., 2016 [36]	USA	Prospective, double-blind, placebo-controlled trial	<u>Exercise group:</u> Mean ± SD 13.6 ± 3.7 <u>Control group:</u> Mean ± SD 13.6 ± 2.9	Exercise group: 22 (56.2%) Control group: 26 (51.5%)	NR	NR	NR	NR	After treatment/ Unspecified	X-ray absorptiometry (DEXA, 4500 QDR-A/Discovery fan beam; Hologic	NR	<u>Exercise group:</u> Mean change (SD) WB BMC/height, total, %: 1.71 (9.01) WB BMD/height, total, %: 6.56 (7.64) LS BMC/height, total, %: 3.70 (21.20) LS BMD/height, total, %: 4.91 (10.34) LS vBMD, %: 5.64 (10.83) <u>Control group:</u> Mean change (SD) WB BMC/height,

Elnaggar et al., 2021 [33]	Saudi Arabia	Prospective, single-blinded quasi-experimental study	<u>Exercise group:</u> Mean ± SD 13.33 ± 3.13 <u>Control group:</u> Mean ± SD 12.87 ± 2.56	Exercise group: 15 (73.3%) Control group: 15 (53.3%)	<u>Exercise group:</u> Mean ± SD 22.53 ± 1.40 <u>Control group:</u> Mean ± SD 21.89 ± 1.57	<u>Exercise group:</u> Mean ± SD 145 ± 14 <u>Control group:</u> Mean ± SD 149 ± 0.13	<u>Exercise group:</u> Mean ± SD 48.20 ± 10.86 <u>Control group:</u> Mean ± SD 49.80 ± 11.54	Exercise group: 15 Acute lymphoblastic leukemia Control group: 15 Acute lymphoblastic leukemia	After treatment/ Unspecified	Lunar DPX-L pediatric software and dual-energy x-ray absorptiometry (DEXA) device (GE-Lunar)	<u>Exercise group:</u> Mean (SD) LS (L_2 through L_5 segment) aBMD (g/cm^2): 0.64 ± 0.10 LS (L_2 through L_5 segment) vBMD (g/cm^3): 0.32 ± 0.04 LS BMC (L_2 through L_5 segment) (g): 33.91 ± 7.12 FN aBMD (g/cm^2): 0.59 ± 0.06 FN vBMD (g/cm^3): 0.31 ± 0.04 FN BMC (g): 32.35 ± 6.69 <u>Control group:</u> Mean (SD) LS (L_2 through L_5 segment) aBMD (g/cm^2): 0.61 ± 0.06 LS (L_2 through L_5 segment) vBMD (g/cm^3): 0.30 ± 0.03 LS (L_2 through L_5 segment) BMC (g/cm): 30.63 ± 5.92 FC aBMD (g/cm^2): 0.62 ± 0.05 FN vBMD (g/cm^3): 0.30 ± 0.04 FN BMC (g): 32.88 ± 6.16	total, %: 3.99 (8.97) WB BMD/height, total, %: 3.45 (7.60) LS BMC/height, total, %: 2.54 (21.06) LS BMD/height, total, %: 5.01 (10.29) LS vBMD, %: 5.30 (11.06) <u>Exercise group:</u> Mean (SD) LS (L_2 through L_5 segment) aBMD (g/cm^2): 0.70 ± 0.06 LS (L_2 through L_5 segment) vBMD (g/cm^3): 0.36 ± 0.03 LS (L_2 through L_5 segment) BMC (g): 37.46 ± 4.59 FN aBMD (g/cm^2): 0.67 ± 0.07 FN vBMD (g/cm^3): 0.34 ± 0.03 FN BMC (g): 37.76 ± 5.65 <u>Control group:</u> Mean (SD) LS (L_2 through L_5 segment) aBMD (g/cm^2): 0.64 ± 0.07 LS (L_2 through L_5 segment) vBMD (g/cm^3): 0.32 ± 0.03 LS (L_2 through L_5 segment)

BMC (g): 33.29 ± 4.14 FC aBMD (g/cm^2): 0.63 ± 0.05 FN vBMD (g/cm^3): 0.31 ± 0.04 FN BMC (g): 34.45 ± 5.02

Abbreviations: RCT: Randomized controlled trial: WB: whole body, LS: lumbar spine; FN: femoral neck; aBMD: areal bone mineral density; vBMD: volumetric bone mineral density; BMAD: bone mineral apparent density; BMC: bone mineral content; SDS: standard deviation scores; NR: Not reported.

Table 2. Intervention characteristics of included studies.

Reference	Frequency (F) Intensity (I) Time (TM) Type (TP)	Volume (V) Progression (P) Intervention Duration (ID) Attendance (A)	Supervision (S) Place of Exercise Program (PEP) Control Group (CG) Other Characteristics (OC)
Hartman et al., 2009 [22]	F: 1/6W (educational sessions), 7/W (functionality maintenance EX) and 2/D (stretching and jumping EX) I: NR TM: NR TP: Education regarding possible motor problems resulting from chemotherapy, EX to maintain hand and leg function and stretching EX to maintain ankle dorsiflexion mobility and short-burst high-intensity EX to prevent reduction in BMD	V: NR P: NR ID: 2 years A: NR	S: No (it was only supervised by their parents) PEP: Home CG: Standard care for the CG included neither an initial session nor any prescheduled follow-up sessions with the hospital-based physiotherapist OC: Parents were supplied with an EX list, enabling them to select EX most appropriate for their child's age and also to vary EX
Müller et al., 2014 [23]	F: During hospital stays: preferably every second day. However, patients had the opportunity to work-out on a daily basis, except for the weekends I: Moderate to vigorous (according to Borg's ratings of perceived exertion of 13–16) TM: 15-45 Min TP: RT	V: 1-3 sets x 6-12 reps P: NR ID: 6 M A: Patients participated in 34.5±8 training sessions on average, corresponding to an adherence rate of 77%, based on the recommendation of training every other day	S: Yes PEP: NR CG: Received standard physiotherapeutic treatment based on their disability and as prescribed by the attending physician daily on workdays and included mobilization techniques of 20–30 Min duration OC: All patients received the same standard physiotherapeutic treatment than the CG. Additionally, sports games like football, basketball or table tennis were offered especially for younger children who could hardly be encouraged for the structured workouts
Cox et al., 2017 [35]	F: 2/W (1^{st} W – 4^{th} W), 1/W (5^{th} W – 8^{th} W) and 1/M (9^{th} W – 135^{th} W) I: - TM: NR TP: Supporting motivation sessions about relatedness, competency, and autonomy	V: - P: No ID: 2.5 years A: There were no differences between the groups relative to APN (P = 0.12) missed appointments (intervention, missed APN visits, mean = 4.39, SD = 5.41; usual care, missed APN visits, mean = 2.49, SD = 3.60	S: No (it could have been supervised by their parents) PEP: Home CG: Usual-care attention control (advanced practice nurse inquired in a neutral manner on the same schedule as for the intervention group) OC: It was emphasized the volitional nature of participation in the program and avoided coercive language)
Waked et al., 2018 [21]	F: 2/W (1^{st}-6^{th} M), 1/W (7^{st}-12^{th} M) I: Light to moderate (according to Borg's ratings of perceived exertion of 3–6 out of 10) TM: 30-45 Min TP: Mixed-modality EX program: 1) AE such as walking or stationary cycling, 2) RT using resistance bands, 3) Flexibility training such as static stretching	V: NR P: Progression of EX for each patient depended on patient tolerance ID: 12 M A: NR	S: Yes PEP: NR CG: Each patient in CG was advised to be active as much as possible OC: Necessary written instructions and tools such as resistance bands for prescribed EX were given to each child

Dubnov-Raz et al., 2015 [24]	F: 3/W I: Moderate TM: 55-60 Min TP: Strength and endurance EX using bands, balls, games, free-weights and various EX machines in the gym	V: NR P: NR ID: 6 M A: NR	S: No PEP: Go-Active gym chain in Israel CG: They were asked to continue with their usual lifestyle habits OC: Adherence to the program was verified by telephone calls to the participants every two W and by periodic visits to the EG
	F: 2/W I: 66–77% of HRpeak (1^{th} W – 4^{th} W), 77– 90% of HRpeak (5^{th} W – 8^{th} W) and 90–100% of HRpeak (9^{th} W – 12^{th} W) TM: 45 Min TP: AE and weight-bearing EX performed in a circuit training-setting with balls, hoops, and running activities	V: NR P: The intensity of the physical EX training program gradually increased ID: 12 W A: The median adherence was 24 sessions (interquartile range (IQR): 20–24). 20 out of 30 children (67%) attended all physical EX training sessions within 12 to 16 W. 13% (9) dropped-out mainly due to recurrence of the disease (7/9)	S: Yes PEP: Local physical therapy practice CG: Usual care according to local guidelines and preferences OC: 10 children (33%) performed some of the EX at a lower heart rate than described
Braam et al., 2018 [34]	F: At least 3/W (7^{th} W – 12^{th} W) I: High intensity TM: 11 Min TP: Weight-bearing EX	V: NR P: No ID: 6 W (from 7^{th} W) A: NR	S: No PEP: Home CG: Usual care according to local guidelines and preferences OC: N
Mogil et al., 2016 [36]	F: 1/W I: - TM: 60 Min TP: Psycho-education and cognitive-behavioral techniques including items on expression of feelings, self-perception and coping skills	V: - P: Yes ID: 12 W A: The psychosocial training intervention was completed by 27 children (90%)	S: Yes PEP: NR CG: Usual care according to local guidelines and preferences OC: After each individual session home EX on the topic of this specific session could be given to the patient if the psychologist considered it necessary
	F: Twice daily I: The mechanical signal (0.3 g at 32-37 Hz) produced a subtle, sinusoidal, vertical translation less than 100 μm via a linear electromagnetic actuator TM: 10 Min TP: Standing on an active platform	V: - P: NR ID: 1 year A: Median (interquartile range) values of 70.1% (35.4%-91.5%) in the intervention and 63.7% (33.3%- 86.5%) in the placebo group (P = .40)	S: No PEP: Home CG: The placebo group stood on a device identical in appearance to the active platform. The placebo device emitted a 500-Hz audible hum but did not deliver the signal OC: Received calcium (800-1200 mg/d) and vitamin D supplements (cholecalciferol, 400 IU/d)
Elnaggar et al., 2021 [33]	F: 3/W I: Weight-bearing TM: 45 Min TP: Lower-body plyometric EX program	V: 10 lower-body Aqua-PLYO EX: 1^{th} W – 4^{th} W: from 1 set x 4 reps to 3 sets x 10 reps 5^{th} W – 8^{th} W: from 1 set x 15 reps to 3 sets x 15 reps 9^{th} W – 12^{th} W: from 2 sets x 10 reps to 5 sets x 10 reps P: The training volume or intensity was increased as the W progressed in three blocks (specifically, every 4 W) ID: 12 W A: The median and interquartile range (IQR) of adherence-to-treatment was 91.67% (IQR 91.67% and 95.83%) in the Aqua-PLYO group and 95.83% (IQR 95.83% and 100%) in the CG	S: Yes PEP: 3 x 4meter water pool CG: Usual physical therapy OC: The water depth was waist-leveled, and the room and water temperature were regulated at 26°C-28°C and 30°C-31°C, respectively

Abbreviations: AE: Aerobic Exercise, EX: Exercise, EG: Exercise Group, HRpeak: Heart Rate Peak, IQR: Interquartile Range, M: Month(s), D: Day, Min: Minutes, NR: Not Reported, N: None, RT: Resistance Training, W: Week.

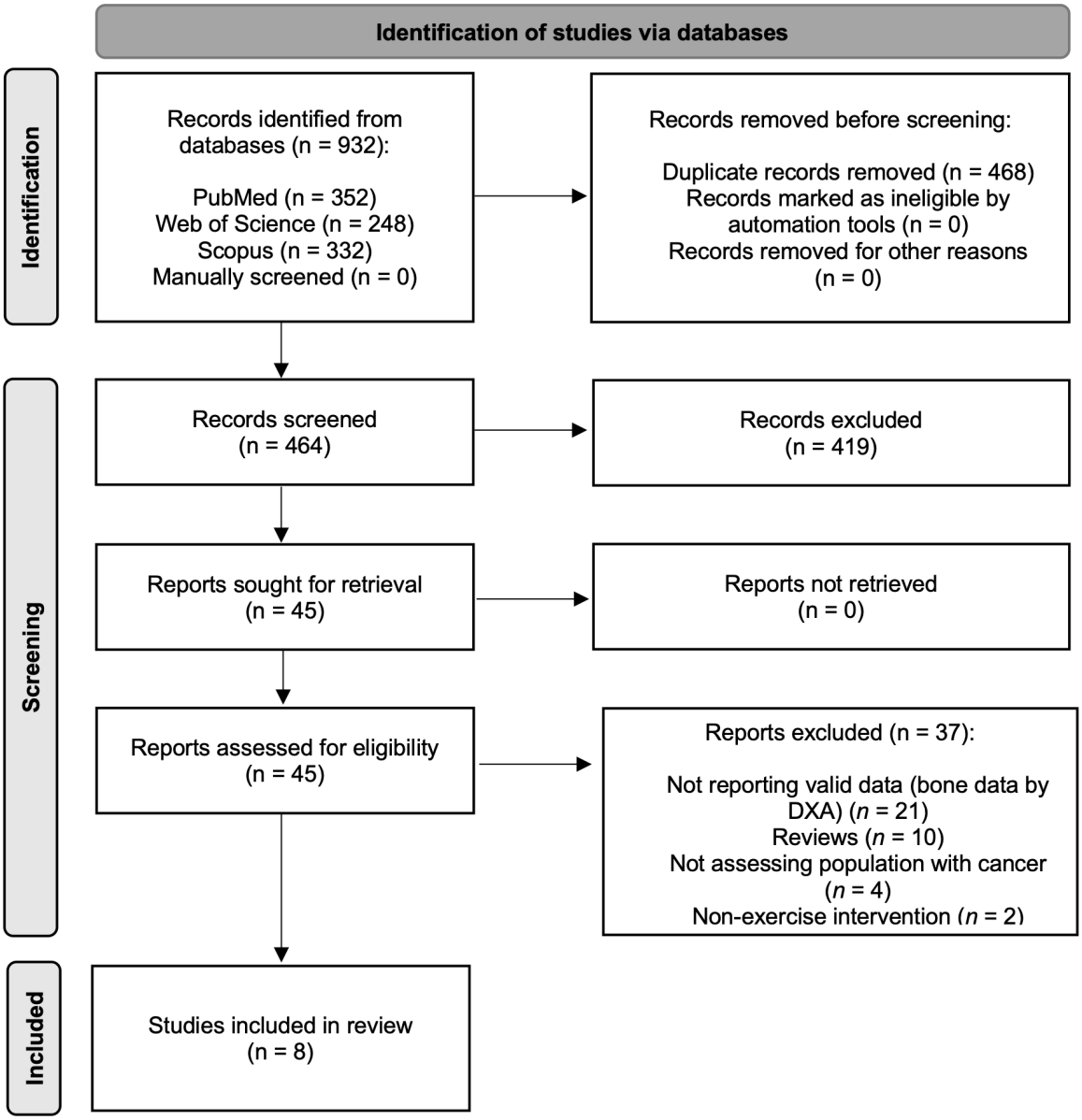

Figure 1. Literature search Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) consort diagram.

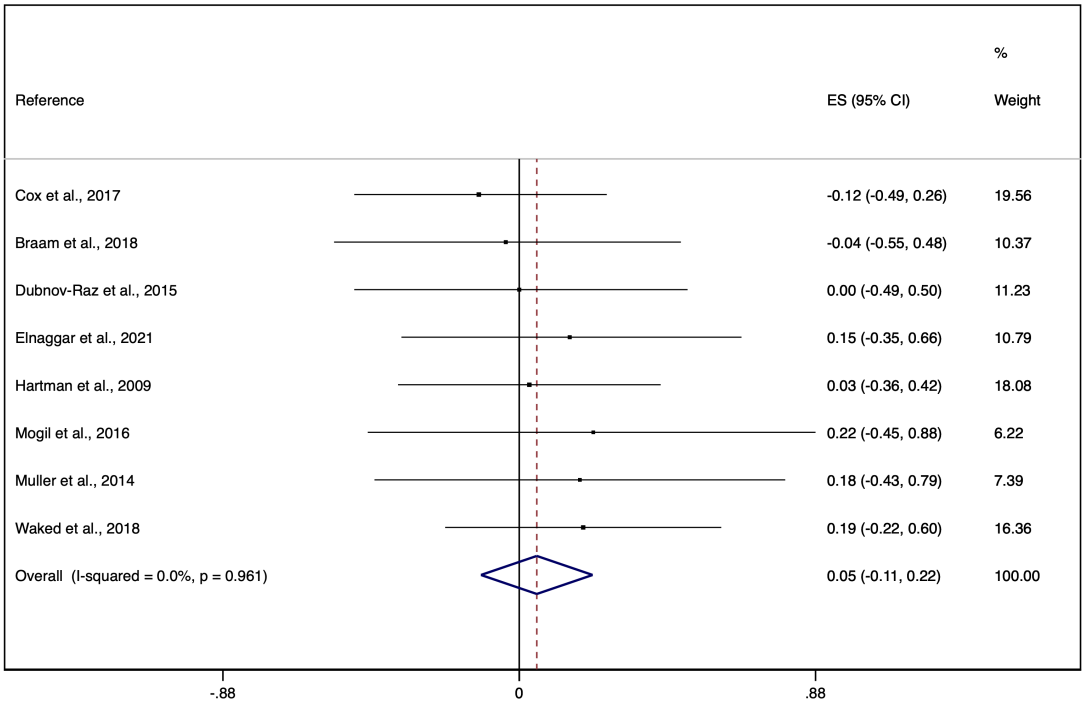

Figure 2. Forest plot of the effect size for the change in total aBMD. CI: confidence interval, ES: effect sizes.

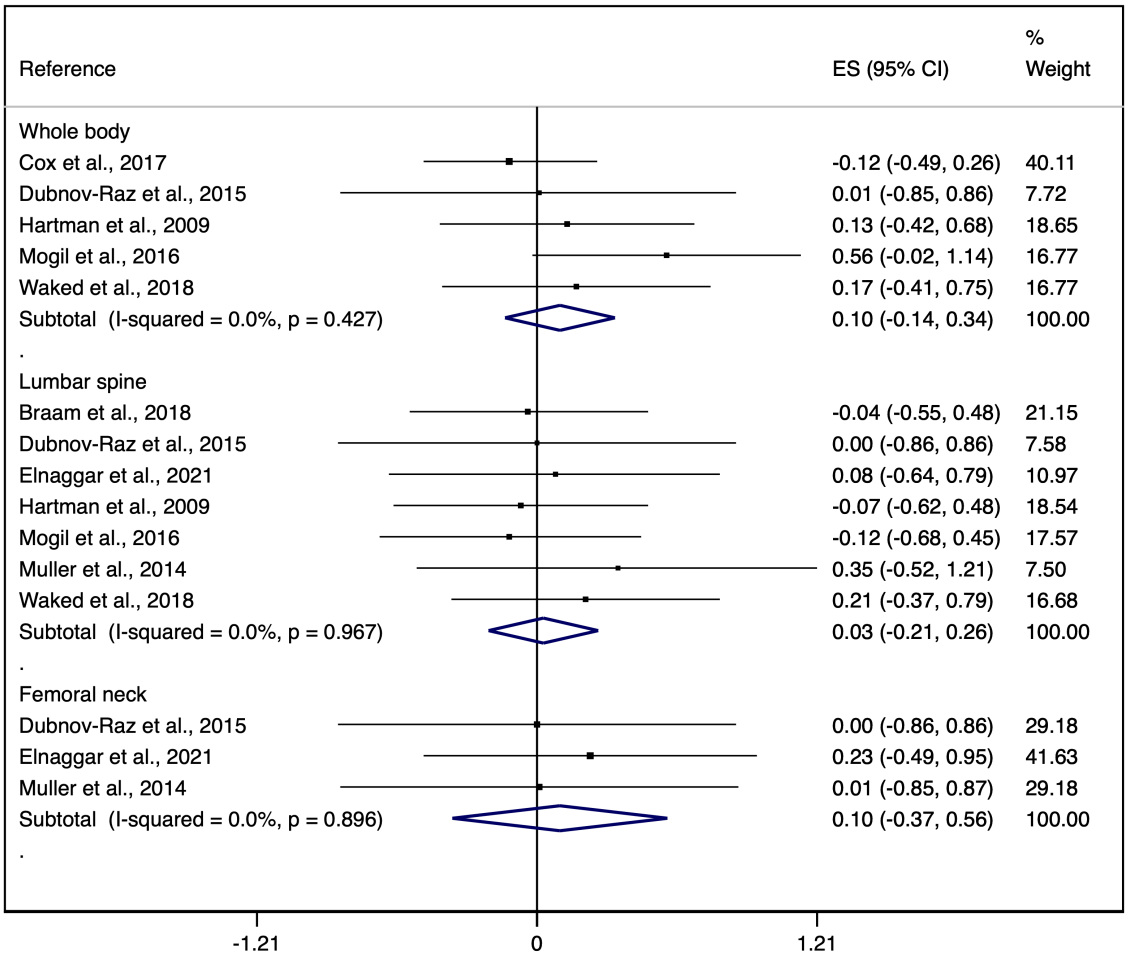

Figure 3. Forest plots of the effect size for the change in aBMD at the whole body, lumbar spine and femoral neck. CI: confidence interval, ES: effect sizes.

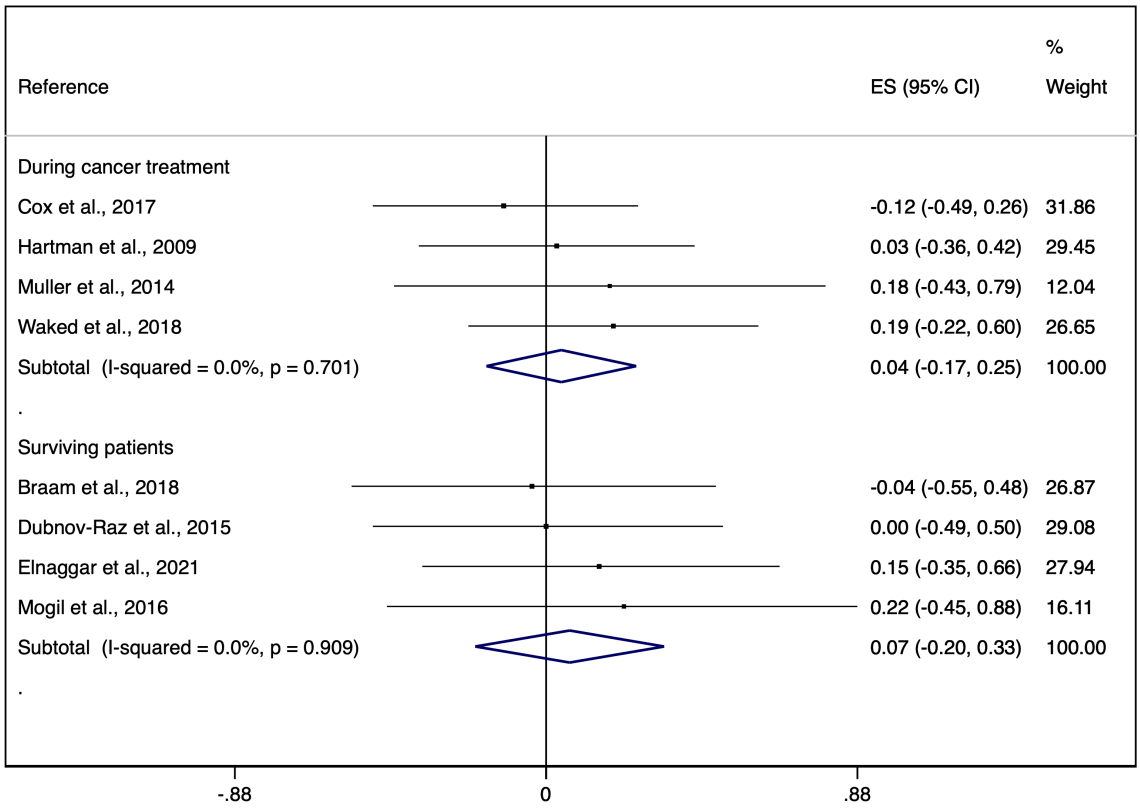

Figure 4. Forest plots of the effect size for the change in aBMD at the whole body, lumbar spine and femoral neck by groups (during cancer treatment and surviving patients). CI: confidence interval, ES: effect sizes.

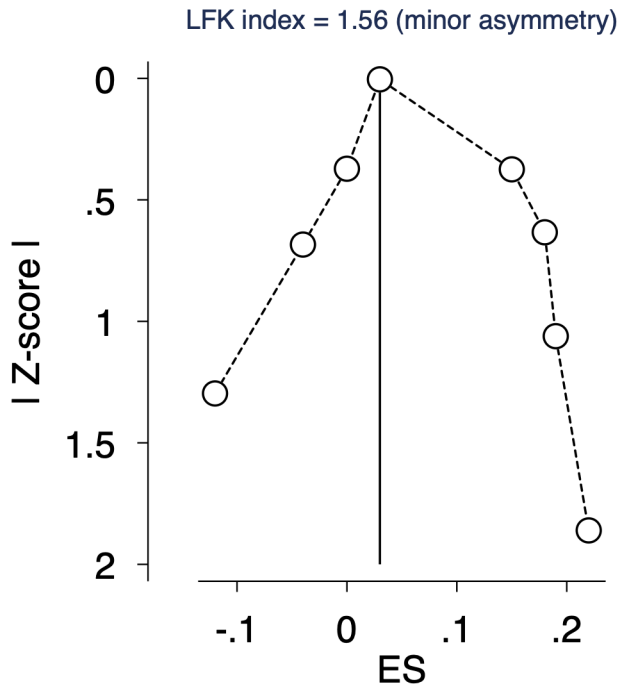

Figure 5. Assessment of potential publication bias by LFK index. Abbreviations: RCT, randomized controlled trial; WB, whole body; LS, lumbar spine; FN, femoral neck; aBMD, areal bone mineral density; vBMD, volumetric bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; SDS, standard deviation scores; NR, Not reported.

Discussion

The findings of the present systematic review and meta-analysis suggest that previous studies are inappropriate to illustrate any beneficial effect on improving bone parameters in children and adolescents during and after oncological treatment. Results should however be interpreted with caution due to the low number of the studies included and the low homogeneity of the intervention characteristics. To the best of our knowledge, this is the first systematic review and meta-analysis synthesizing the evidence on the effect of exercise on bone health in children and adolescents during and after oncological treatment.

During oncological treatment, there are no studies showing a beneficial effect of exercise on bone parameters in children and adolescents. First and foremost, one of the most common side effects during oncological treatment is cancer-related fatigue [37,38]. This may be reflected by the poor adherence of participants to the exercise intervention as in the study of Hartman et al. [22], in which 36% of participants exercised less than once a week. This could have been an important barrier to achieve the required exercise intensity to effectively stimulate the bone and to obtain bone adaptations. As an example, previous research in healthy adolescents showed that those who did 28-32 minutes of vigorous physical activity per day had optimal aBMD at key regions within the hip [39]. Secondly, the prescribed exercise type might not be appropriate to bone adaptations in some studies. For instance, despite weight-bearing and impact exercises of high intensity significantly contribute bone development, this type of exercise was not chosen in the studies of Müller et al. [23] and Waked [21,35], and when included, the intensity required to modify bone parameters were not achievable as mentioned in the study of Cox et al. [35]. The latter intervention was proven not to be feasible during the early oncological treatment phase owing to the child's responses to the disease and the treatment. Interestingly, this exercise intervention was the longest (30 months) in comparison with the rest of studies. Finally, it is important to mention that half of the exercise interventions were unsupervised [22,35], which does not concur with the International Pediatric Oncology Exercise Guidelines which recommend that a qualified exercise professionals should implement supervised exercise program throughout cancer continuum [40].

To sum up, the most updated research in children and adolescents during oncological treatment suggests that there is no evidence of an effect of exercise at inducing meaningful bone adaptations. Overall, the potential cancer-related fatigue sequel, the selection of the inappropriate exercises to improve bone parameters (i.e., cycling, lack of weight-bearing impact exercises of high intensity, unsupervised exercise interventions) and the unachievable intensity of the interventions are important factors that have hindered the required stimulus in

the bones. The use of behavior change techniques (i.e., gamification) in long-lasting interventions with growing population is recommended [41,42] and could have helped to increase the low adherence rate reported [22,35].

Shortly after oncological treatment, there is no evidence of positive effects of exercise interventions aimed at improving bone parameters. One of the potential factors could be the short duration as half of the interventions lasted for only three months [33,34]. The bone remodeling process takes approximately 5 months and therefore, shorter interventions could not reflect true bone adaptations [43]. In addition, the type of exercise has not been the most appropriate to improve bone parameters in some cases. Dubnov-Raz et al. [24] did not include weight-bearing impact exercises of high intensity, yet participants reported to be mentally and physically healthier than those in previous studies during oncological treatment [35]. Likewise, Elnaggar et al. [33] included lower-body plyometric exercises in a swimming pool, that is, in a microgravity environment, which is not effective at increasing bone parameters [44]. Nevertheless, Mogil et al. [36] implemented an intervention including standing on an active vibration platform emitting low-magnitude high-frequency mechanical stimulation, considered a type of weight-bearing physical activity as it requires muscles and bones to work against gravity [45,46]. From the included studies, the latter was the only intervention that observed a borderline significant increase in total body aBMD ($p=0.05$). The timing of the intervention (i.e., after oncological treatment), the frequency (twice per day) and adequate intervention duration (one year) could explain the findings. However, their intervention type was clearly ineffective at increasing lumbar spine aBMD outcomes. As stated by the authors, this might have been caused by the potential loss of vibratory energy as the signal travelled from the distal lower extremity to the trunk. This agrees with a recent systematic review and meta-analysis in children and adolescents with motor disabilities that found no pooled effect of similar interventions on lumbar spine aBMD [47]. Lastly, some studies did not exclude participants receiving growth hormone, corticosteroids or bisphosphonates [24], or even included participants during the remaining oncological treatment period [34], which might have affected the results.

In conclusion, there is no evidence of an effect of exercise interventions conducted after oncological treatment at increasing bone parameters in children and adolescents. There are several reasons that may explain this lack of effect: the short duration of the interventions, the type of the exercises (i.e., lack of weight-bearing exercises or in a microgravity environment) and inclusion of participants undergoing maintenance treatment that affects bone parameters.

Remarkably, the exercise interventions were not delivered by exercise professionals in 75% of the included studies. This sets a potential barrier and limitation for the intervention to succeed. There is a need of exercise professionals with a high qualification and robust background in exercise oncology. Similar thoughts have been shared by Adams et al. [48] who stated that oncologic healthcare providers working in cancer care system did not feel confident when prescribing exercise and therefore, they should not be responsible for prescribing it. According to the International Pediatric Oncology Exercise Guidelines, qualified exercise professionals should be part of standard care and therefore should facilitate program implementation and uptake throughout the cancer continuum [40].

The present systematic review and meta-analysis has several limitations. The main limitation is the availability of published studies and well-designed RCTs aiming at investigating bone changes in children and adolescents diagnosed with cancer. Additionally, the data reported were exclusively taken from the manuscripts included in this work and not from the clinical trials registries. In most of the cases, the interventions were not designed to meet the aim of improving bone health. Thus, these findings should be viewed with caution. Nevertheless, it shows the current evidence on exercise paediatric oncology and bone health and should be viewed as a starting point for researchers to think of the best approach for designing their exercise interventions. To date, only two systematic reviews and meta-analyses have been conducted with the same purpose in adult cancer patients during and after oncological treatment with promising positive results [49,50].

Conclusion

Our systematic review and meta-analysis indicate that the exercise interventions were inappropriate and therefore, ineffective to illustrate any beneficial effect on bone of children and adolescents with cancer during and after oncological treatment. Several limitations in the design of the interventions have been identified. There is a need of implementing well-designed exercise RCTs specifically focused on improving bone health in children and adolescents diagnosed with cancer due its scientific and clinical importance. Early intervention strategies to optimize bone health through effective tailoring of osteogenic exercise program are of vital importance.

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Supplementary material

Table S1. PRISMA 2020 Checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 64
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 64
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 65
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 65-66
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pages 66-67
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 66
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 66 and Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 66-67 and Figure 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pages 67-68
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pages 66-68
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pages 66-68
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 67-68 and Table S3-4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Table 1
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pages 67-68

Section and Topic	Item #	Checklist item	Location where item is reported
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pages 67-69
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pages 67-69
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pages 67-69
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pages 67-69
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pages 67-69
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pages 67-69
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pages 67-69
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 69 and Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Page 69 and Tables 1 and 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 69 and Table S3-4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figures 2-4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 69 or Table S3-4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figures 2-5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pages 69-71 and Figure 5
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pages 69-71
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Figure 5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	No applicable

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 85
	23b	Discuss any limitations of the evidence included in the review.	Page 87
	23c	Discuss any limitations of the review processes used.	Page 87
	23d	Discuss implications of the results for practice, policy, and future research.	Pages 85-87
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 66
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 66
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 66
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Yes
Competing interests	26	Declare any competing interests of review authors.	No
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	No applicable

Table S2. Search terms used in databases.

MEDLINE (via PubMed)
(exercis*[Title/Abstract] OR move*[Title/Abstract] OR moving[Title/Abstract] OR sport*[Title/Abstract] OR train*[Title/Abstract] OR "physical activity"[Title/Abstract] OR weightbear*[Title/Abstract] OR "high impact"[Title/Abstract] OR running[Title/Abstract] OR walk*[Title/Abstract] OR strength*[Title/Abstract] OR "physical fitness"[Title/Abstract] OR step*[Title/Abstract] OR gymnastic[Title/Abstract] OR balance[Title/Abstract]) AND (bone[Mesh] OR bone[Title/Abstract]) AND (cancer[Title/Abstract] OR oncology[Mesh] OR onco*[Title/Abstract] OR myelo*[Title/Abstract] OR leukaemia[Title/Abstract] OR leukemia[Title/Abstract] OR neoplasm*[Title/Abstract] OR lympho*[Title/Abstract] OR carcinoma[Title/Abstract] OR tumor[Title/Abstract] OR tumour[Title/Abstract] OR sarcoma[Title/Abstract]) AND (child*[Title/Abstract] OR adolescen*[Title/Abstract] OR young*[Title/Abstract] OR boy*[Title/Abstract] OR girl*[Title/Abstract] OR pediatric*[Title/Abstract] OR paediatric*[Title/Abstract]) AND (trial*[Title/Abstract] OR random[Title/Abstract] OR intervention*[Title/Abstract] OR program*[Title/Abstract] OR rehabilitation[Title/Abstract])
Web of Science
AB=((exercis* OR move* OR moving OR sport* OR train* OR "physical activity" OR weightbear* OR "high impact" OR running OR walk* OR strength* OR "physical fitness" OR step* OR gymnastic OR balance) AND (bone) AND (cancer OR onco* OR myelo* OR leukaemia OR leukemia OR neoplasm* OR lympho* OR carcinoma OR tumor OR tumour OR sarcoma) AND (child* OR adolescen* OR young* OR boy* OR girl* OR pediatric* OR paediatric*) AND (trial* OR random OR intervention* OR program* OR rehabilitation))
Scopus
(TITLE-ABS(exercis*) OR TITLE-ABS(move*) OR TITLE-ABS(moving) OR TITLE-ABS(sport*) OR TITLE-ABS(train*) OR TITLE-ABS("physical activity") OR TITLE-ABS(weightbear*) OR TITLE-ABS("high impact") OR TITLE-ABS(running) OR TITLE-ABS(walk*) OR TITLE-ABS(strength*) OR TITLE-ABS("physical fitness") OR TITLE-ABS(step*) OR TITLE-ABS(gymnastic) OR TITLE-ABS(balance)) AND (TITLE-ABS(bone)) AND (TITLE-ABS(cancer) OR TITLE-ABS(onco*) OR TITLE-ABS(myelo*) OR TITLE-ABS(leukaemia) OR TITLE-ABS(leukemia) OR TITLE-ABS(neoplasm*) OR TITLE-ABS(lympho*) OR TITLE-ABS(carcinoma) OR TITLE-ABS(tumor) OR TITLE-ABS(tumour) OR TITLE-ABS(sarcoma)) AND (TITLE-ABS(child*) OR TITLE-ABS(adolescen*) OR TITLE-ABS(young*) OR TITLE-ABS(boy*) OR TITLE-ABS(girl*) OR TITLE-ABS(pediatric*) OR TITLE-ABS(paediatric*)) AND (TITLE-ABS(trial*) OR TITLE-ABS(random) OR TITLE-ABS(intervention*) OR TITLE-ABS(program*) OR TITLE-ABS(rehabilitation))

Table S3. Quality assessment of included articled for Randomized Controlled Trials.

Table S4. Quality assessment of included articles for Quasi-Experimental Studies.

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Quality Category
Dubnov-Raz, 2015	✓	✓	×	✓	✓	✓	✓	✓	×	High
Elnaggar, 2021	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Müller, 2014	✓	×	×	✓	✓	✓	✓	✓	×	Medium
Criterion Score %	100	66.67	33.33	100	100	100	100	100	33.33	

Note that the criterion score is calculated by dividing the number of studies meeting one criterion by the total number of studies. ✓: meet the methodological quality criterion; ×: not meet the methodological quality criterion.; ?: unclear; N/A: not applicable.

Chapter 5. Determinants of bone parameters in young paediatric cancer survivors: The iBoneFIT Project

Abstract

Background. Bone health is remarkably affected by endocrine side effects due to paediatric cancer treatments and the disease itself. We aimed to provide novel insights into the contribution of independent predictors of bone health in young paediatric cancer survivors.

Methods. This cross-sectional multicenter study was carried out within the iBoneFIT framework in which 116 young paediatric cancer survivors (12.1±3.3 years old; 43% female) were recruited. The independent predictors were sex, years from PHV, time from treatment completion, radiotherapy exposure, region-specific lean and fat mass, musculoskeletal fitness, moderate-vigorous physical activity and past bone-specific physical activity.

Results. Region-specific lean mass was the strongest significant predictor of most aBMD, all hip geometry parameters and TBS (β=0.400–0.775, $p \leq 0.05$). Years from PHV was positively associated with total body less head, legs and arms aBMD, and time from treatment completion was also positively associated with total hip and femoral neck aBMD parameters and, narrow neck cross-sectional area (β=0.327–0.398, $p \leq 0.05$; β=0.135–0.221, $p \leq 0.05$), respectively.

Conclusion. Region-specific lean mass was consistently the most important positive determinant of all bone parameters, except for total hip aBMD, all HSA parameters and TBS.

Introduction

Paediatric cancer survival has experienced an unparallel increase during the last years [1]. The 5-year survivorship rate for all paediatric cancers has approached 85% [2]. However, a low aBMD, defined by a Z-score less than -1, has been found in up to 68% of young paediatric cancer survivors while a very low aBMD (Z-score less than -2) was found in up to 46% of them [3]. This is caused by decreased bone formation and increased bone resorption due to paediatric cancer treatments and the disease itself [4]. Remarkably, paediatric cancer occurs during a critical time of active skeletal maturation and growth, affecting the accrual of bone mass and therefore, bone preservation throughout life [5].

Physical activity has become a cornerstone as an effective strategy to develop healthy bones during childhood and adolescence [6], mainly when high-impact weight-bearing physical activity occurs above a certain intensity and duration [7]. Following cancer diagnosis, children and adolescents with low physical activity levels are more prone to have increased bone resorption and, consequently, limited bone mass quantity and quality [4]. A previous study showed positive associations between physical activity and lumbar spine aBMD among Wilms tumour survivors [8]. Physical activity contributes to the development of bone mass due to its association with increases in lean mass according to Frost's mechanostat theory, which states that bigger muscles exert higher tensile forces on the bones they attach [9]. Likewise, musculoskeletal fitness seems to be an important factor for developing and preserving normal aBMD in paediatric cancer survivors [10]. This relationship may be explained as well by improvements in lean mass [11]. Poor lean mass has been recognised as a risk factor that contributes to bone pathology during and after oncological treatment in young paediatric cancer survivors [12]. Other modifiable factors, such as calcium intake [13] and vitamin D status [14], are known to be essential components of bone formation during childhood and adolescence. Previous evidence has found vitamin D deficiency in children after cancer diagnosis [15] and a recent review of the literature underlined that about 70% of the paediatric cancer survivors did not meet the Recommended Dietary Allowance for calcium [16]. Nevertheless, the integrative and quantitative contribution of these factors on bone parameters in young paediatric cancer survivors remains unknown [12]. Previous evidence identified that lean mass is the most important predictor of bone parameters in healthy and athletic children and adolescences [17], but it remains unknown whether other factors could outweigh the contribution of lean mass in young paediatric cancer survivors.

In this study, we aim to provide novel insights into the contribution of independent predictors to bone parameters in young paediatric cancer survivors. In order to provide a more in-depth

evaluation of the bone status of this population, we included not only aBMD outcomes obtained by DXA, but also other DXA-derived parameters obtained from the HSA and the textural analysis of the lumbar spine. We hypothesized that region-specific lean mass and years from PHV would be the most important contributors of bone parameters in young paediatric cancer survivors, as in healthy young population [17].

Methods

Study design and participants

This observational study was developed within the iBoneFIT project framework (https://profith.ugr.es/pages/investigacion/proyectos/ibonefit). A detailed description of the methodology was carried and described elsewhere [18]. In short, iBoneFIT is a multicentre parallel group randomised controlled trial designed to examine the effect of a 9-month online exercise programme on bone health in young paediatric cancer survivors aged 6-18 years [18]. Young paediatric cancer survivors were recruited from the Units of Paediatric Oncology and Haematology of the 'Virgen de las Nieves' (Granada) and 'Reina Sofia' (Cordoba) University Hospitals. Inclusion criteria were: i) being six to eighteen years old; ii) not currently receiving treatment for cancer; iii) diagnosed one year earlier at minimum; and iv) to have been exposed to radiotherapy and/or chemotherapy. Participants were recruited in the iBoneFIT project between Autumn and Winter from October 2020 and March 2022 in two waves. All parents and participants provided written consent and assent, respectively. iBoneFIT was approved by the Ethics Committee on Human Research of Regional Government of Andalusia (Reference: 4500, December 2019), followed the ethical guidelines of the Declaration of Helsinki (revised version 2013) and was registered in ClinicalTrials.gov (identifier: isrctn61195625, 2 April 2020). This study followed the STROBE checklist (Strengthening The Reporting of OBservational Studies in Epidemiology) [19] (**Table S1**). Although we recruited 116 participants in total, sample size slightly varied in some variables due to missing data (i.e., some participants were unable to perform some of the tests, were afraid of being scanned using DXA or not willing to collaborate on testing day).

Descriptive characteristics

Anthropometry and somatic maturity

Body mass (kg) was assessed with an electronic scale (SECA 861, Hamburg, Germany) with an accuracy of 100 g. Stature (cm) was assessed using a precision stadiometer (SECA 225,

Hamburg, Germany) to the nearest 0.1 cm. Somatic maturity was measured using the prediction of years from PHV using validated algorithms for males and females [20].

Clinical data

Information about the type of cancer (**Table S2**), type of treatment (radiotherapy, chemotherapy and/or surgery, alone or in combination) and time from treatment completion was obtained from the participants' medical records. Since radiotherapy is a strong risk factor for persistently low BMD (Z-score less than -1) in young paediatric cancer survivors [21], a dichotomic variable based on the type of treatment (radiotherapy; yes/no) was computed and used as a predictor variable. Moreover, we observed in a preliminary analysis that this variable was more correlated with bone outcomes than type of cancer, and hence, the later was not included in the regression models.

Physical activity

Participants were given a tri-axial accelerometer (ActiGraph GT3X, Pensacola, FL) to be worn in their non-dominant wrist for at least seven consecutive days (24 hours a day). They only removed it for water-based activities (e.g. bathing or swimming). Moreover, participants had a diary to record the time when they went to bed, woke up and removed the device. Accelerometers were initialised at a sampling frequency of 90 Hz and raw data were processed as described elsewhere [22]. Daily means were used for the analyses (min/day). MVPA was used in preference to other intensities due to its health-related benefits. A valid day was considered when the accelerometer registered at least 23 hours and the participants wore it at least for 16 hours. Additionally, no distinction was made between weekdays and weekends since there were no significant differences between MVPA weighted and plain variables in our sample. Five seconds epochs after auto-calibration of the raw acceleration were applied and the cut-off point for MVPA was 200 mg [23]. Daily means were used for the analyses (min/day).

Using the bone-specific physical activity questionnaire [24], the past activity was reported by the participants taking into account which sport they had practised throughout their lifespan and for how long. The (past) bone-specific physical activity questionnaire algorithm is obtained as follows: R x y x a, where R refers to the effective load stimulus (derived from ground reaction force testing), y refers to the years of participation, and a refers to the age weighting factor (participants < 15 years = 0.25; participants > 15 years = 0.1). This tool has been validated to assess the osteogenic characteristics of previous sports and physical activities on the skeleton [24].

Musculoskeletal fitness

Upper-body strength was obtained using the handgrip test (performed twice by each hand and the best scores were averaged) and lower-body power using the standing long jump test (performed twice and the best score was retained) according to the ALPHA health-related fitness test battery for children and adolescents [25]. These field-based fitness tests have been validated, reliable and related to health in children and adolescents [26].

Calcium and vitamin D

Daily calcium intake (in milligrams) and vitamin D status were estimated by validated food-frequency questionnaires, respectively [27,28]. Vitamin D status was based on three questions regarding sun exposure during the last year for any time (yes/no), use of tanning booth (yes/no) and the number of glasses of milk per day (two or more glasses were considered as yes and less than two glasses were considered as no). Using the threshold of two out of three negative responses for these habits proposed by [28], we identified participants with vitamin D deficits.

Body composition

Dual-energy X-ray absorptiometry (DXA)

A single DXA scanner (Hologic Series Discovery QDR, Bedford, MA) and the APEX software (version 4.0.2) were used to perform three scans (total body, right hip and lumbar spine) and obtain aBMD (g/cm^2) of the total body less head, femoral neck, lumbar spine (mean of L1-L4), total hip, legs and arms. Following the International Society of Clinical Densitometry recommendations for paediatric population [29], total body less head values were used in preference to total body. The total body scan was also used to obtain lean mass (g) [body mass–(fat mass+bone mass)] and fat mass (g) of the total body less head, trunk, legs and arms. The device was calibrated every single day using a lumbar spine phantom. The positioning of the participants remaining still and in the supine position, and the analyses of the results were undertaken according to the International Society of Clinical Densitometry [29].

A single trained researcher analysed all DXA scans to standardise the analyses performed by three trained assessors. Previous paediatric populations studies have shown the percentage coefficient of variation of the DXA between 1.0 and 2.9%, depending on the region [30].

Hip Structural Analysis (HSA)

Hip geometry parameters at the narrowest point of the femoral neck were determined using HSA software (based on DXA images of the hip analysis) which analyses structural characteristics in a line of pixels across the bone axis through the distribution of bone mineral mass [31]. We obtained the following estimates: (1) cross sectional area (cm^2), provides a score of axial compression strength of the bone surface area in the cross-section after excluding soft tissue and trabecular space; (2) cross sectional moment of inertia (cm^4), which is the index of structural rigidity and; (3) section modulus (cm^3), which is the bending strength indicator for maximum bending stress in the direction of the image plane. The short-term precision percentage coefficient of variation of these variables has been reported to be between 2.4 and 6.4% [32].

Trabecular Bone Score (TBS)

This iNsight Software (Medimaps, research version 3.0, Pessac, France) that indirectly provides a textural index of trabecular microarchitecture in the lumbar spine. This DXA-based technological tool is considered a score of bone quality since it has been shown to significantly predict fracture risk [33]. TBS determines the heterogeneity of the grey-levels pixels of the aBMD lumbar spine and lower homogeneity implies worse trabecular connectivity based on experimental variograms of the projected DXA image [34]. All calculations were performed at the aBMD lumbar spine assessed by the same trained researcher. The short-term coefficient of variation for TBS has been reported to be between 1.7 and 2.1% for lumbar spine aBMD [35]. Although TBS has been mostly used in adult population [36], its use has been extended into paediatric population in the last years [37-39].

Statistical analysis

The normal distribution of the raw variables was checked and verified using visual check of histograms, skewness and kurtosis values, Shapiro-Wilk test, Q-Q and box plots. Descriptive data were illustrated as mean and SD. Collinearity was checked for the variables using the variance inflation factor (VIF) and tolerance levels. Missing data were not imputed.

Multiple linear regression analyses were conducted to ascertain the contribution of sex, years from PHV, time from treatment completion, radiotherapy exposure, region-specific lean and fat mass, upper-body strength, lower-body power, MVPA and past bone-specific physical activity to the variance of total and regional aBMD, HSA parameters and TBS. Region-specific lean mass and region-specific fat mass were used as predictor variables because of the site-specific adaptations on the skeleton [17], as follows; the legs lean mass or fat mass were used

as predictor variables for hip-related bone outcomes; the arms lean mass or fat mass were used as predictor variables when the outcome was the arms aBMD and; the trunk lean mass or fat mass were used as predictor variables for lumbar spine bone outcomes. Sex-interaction was checked for the associations between predictors and dependent variables. No interaction was found in most of them and therefore analyses were conducted for males and females together and sex was added as a potential predictor. The selection of the predictor variables was based on their relationship with bone parameters [17,40-42]. In a preliminary analysis we found that calcium intake and vitamin D status were not significant predictors of bone parameters in this population (**Table S3**) and consequently they were not included in the model. The remaining predictors were entered into the regression models simultaneously. Consequently, the sample size dropped from 116 to 98-99 participants (depending on the outcome variable) because the regression analysis in the Statistical Package for the Social Sciences (IBM Corporation, Chicago, Illinois) takes the lowest sample of participants with data in all the studied variables. For the multiple linear regressions, the standardised β coefficients was presented, R^2 was calculated by the Stein´s equation [43] as it shows how well the models predict the values of a different sample from the same population and values of 0.05 were considered statistically significant. The squared semi-partial correlation coefficients (sr^2) were included to quantify the contribution of each predictor in the overall variance of the model removing shared contributions with other predictors.

Results

A total of 116 young paediatric cancer survivors (12.1±3.3 years old; 43% female) were recruited. **Table 1** shows descriptive characteristics of the participants included in this study. Most of the participants were diagnosed with acute lymphoblastic leukaemia (38.8%), lymphoma (12.0%) and central nervous system (9.5%) (**Table S2**).

Determinants of areal bone mineral density (aBMD)

Multivariate regression models for aBMD parameters significantly explained 55.3%-84.0% (on average, 69.7%) of the variance in the aBMD parameters (**Table 2**). Region-specific lean mass was the strongest significant predictor and was positively associated with all aBMD parameters (β=0.400–0.517, sr^2=0.017–0.023, $p \leq 0.05$), except for total hip ($p > 0.05$). Years from PHV was positively associated with aBMD at total body less head, legs and arms (β=0.327–0.398, sr^2=0.016–0.027, $p \leq 0.05$). Past bone-specific physical activity was positively associated with aBMD at total hip and arms (β=0.097–0.162, sr^2=0.006-0.018, $p \leq 0.05$). Being

female was positively associated with aBMD at lumbar spine (β=0.182, sr^2=0.017, p≤0.05). Time from treatment completion was positively associated with aBMD at total hip (β=0.221, sr^2=0.037, p≤0.05). Fat mass was positively associated with aBMD at arms (β=0.232, sr^2=0.028, p≤0.05). Radiotherapy exposure, upper-body strength, lower-body power and MVPA were not found to be significant predictors of aBMD parameters (all β coefficient<0.137, p>0.05). The contribution of each predictor variable by its standardised β coefficient to each bone parameter is visually displayed in **Figure S1**.

Determinants of Hip Structural Analysis parameters and Trabecular Bone Score

In the multivariate regression analysis of the HSA (**Table 3**), the predictors explained 43.9%-64.6% (on average, 54.25%) of the variance in the HSA and TBS. Region-specific lean mass was the strongest significant predictor and was positively associated with all HSA parameters (β=0.628–0.775, sr^2=0.049–0.071, p≤0.05). Being female (positively) and upper-body strength (negatively) were associated with TBS (β=0.245 and -0.443, sr^2=0.031 and 0.023, p≤0.05, respectively). Time from treatment completion was positively associated with narrow neck cross sectional area (β=0.135, sr^2=0.014, p≤0.05). Years from PHV, radiotherapy exposure, fat mass, lower-body power, MVPA and past bone-specific physical activity were not found to be significant predictors of the HSA parameters nor spine TBS (all β coefficient<0.246, p>0.05). The contribution of each predictor variable by its standardised β coefficient to each bone parameter is visually displayed in **Figure S2**.

Table 1. Descriptive characteristics of the participants included in this study.

Variable	Total	N	Females	N	Males	N
Sex (female/male, %)	43/57	116				
Age (years)	12.1 (3.3)	116	12.3 (3.5)	50	12.0 (3.2)	66
Body mass (kg)	46.6 (18.0)	116	46.0 (19.0)	50	47.1 (17.4)	66
Stature (cm)	147.5 (17.1)	116	145.6 (16.0)	50	148.9 (17.8)	66
Body mass index (kg/m^2)	20.7 (4.7)	116	20.9 (5.3)	50	20.5 (4.1)	66
Time from treatment completion (years)	5.1 (3.9)	114	5.3 (4.2)	49	5.0 (3.7)	65
Radiotherapy exposure (yes/no)	32/84	116	13/37	50	19/47	66
Years from peak height velocity	-0.8 (2.7)	116	0.0 (2.9)	50	-1.4 (2.5)	66
Calcium intake (mg/day)	785.5 (437.2)	116	702.94 (384.6)	50	848.02 (466.7)	66
Vitamin D status (yes/no, %)	53.2/46.8	111	60.4/39.6	48	47.6/52.4	63
Fitness and Physical Activity						
Upper-body strength (kg)	18.1 (8.6)	116	16.32 (5.92)	50	19.39 (10.01)	66
Lower-body power (cm)	118.1 (33.1)	115	106.4 (25.1)	50	127.2 (35.8)	65
Moderate-to-vigorous physical activity (min)	41.6 (25.7)	110	35.9 (25.2)	49	46.2 (25.4)	61
Number of valid days	7.5 (0.8)	110	7.3 (1.0)	49	7.6 (0.5)	61
Past bone-specific physical activity	12.6 (16.0)	108	9.7 (13.4)	46	14.7 (17.3)	62
Lean Mass (g)						
Total body less head	25713.2 (10381.1)	116	23937.8 (8962.5)	50	27058.1 (11218.3)	66
Legs	4560.9 (1950.3)	116	4187.2 (1591.7)	50	4844.1 (2152.1)	66
Arms	1338.5 (587.3)	115	1166.2 (444.9)	49	1466.4 (647.9)	66
Trunk	14296.0 (5561.0)	116	13611.4 (5129.4)	50	14814.7 (5852.0)	66
Fat Mass (g)						
Total body less head	14899.1 (8336.3)	116	16161.2 (9695.7)	50	13942.9 (7066.0)	66
Legs	3227.5 (1644.7)	116	3493.7 (1816.4)	50	3025.8 (1484.2)	66
Arms	896.6 (535.0)	115	987.1 (653.7)	49	829.4 (419.1)	66
Trunk	6644.3 (4171.0)	116	7187.7 (4932.0)	50	6232.6 (3470.3)	66
Areal bone mineral density (g/cm^2)						
Total body less head	0.791 (0.159)	116	0.791 (0.163)	50	0.791 (0.157)	66
Femoral neck	0.732 (0.152)	115	0.744 (0.176)	49	0.723 (0.132)	66
Lumbar spine	0.731 (0.187)	116	0.776 (0.195)	50	0.697 (0.175)	66
Total hip	0.823 (0.169)	115	0.819 (0.185)	49	0.825 (0.158)	66
Legs	0.924 (0.200)	116	0.919 (0.203)	50	0.927 (0.200)	66
Arms	0.595 (0.116)	115	0.580 (0.119)	49	0.605 (0.114)	66
Hip Structural Analysis						
Narrow neck cross-sectional area (cm^2)	2.203 (0.677)	115	2.147 (0.682)	49	2.244 (0.675)	66
Narrow neck cross-sectional moment of inertia (cm^4)	1.378 (0.861)	115	1.192 (0.611)	49	1.516 (0.989)	66
Narrow neck section modulus (cm^3)	0.871 (0.416)	115	0.807 (0.357)	49	0.918 (0.452)	66
Trabecular Bone Score	1.318 (0.103)	116	1.348 (0.112)	50	1.296 (0.089)	66

Data are presented as mean (standard deviation) or as frequencies (associated percentages), as indicated.

Table 2. Multiple regressions models for areal bone mineral density (aBMD) parameters.

	Predictors	β	sr^2	*P*		Predictors	β	sr^2	*P*
TBLH aBMD (R^2=0.823) N = 99	Sex	0.029	0.000	0.610	Total Hip aBMD (R^2=0.598) N = 98	Sex	0.106	0.006	0.216
	Years from peak height velocity	**0.344**	**0.018**	**0.001**		Years from peak height velocity	0.146	0.003	0.356
	Time from treatment completion	0.029	0.001	0.543		**Time from treatment completion**	**0.221**	**0.037**	**0.002**
	Radiotherapy exposure	-0.022	0.000	0.612		Radiotherapy exposure	0.020	0.000	0.765
	Total body less head lean mass	**0.493**	**0.022**	**<0.001**		Legs lean mass	0.273	0.009	0.117
	Total body less head fat mass	0.122	0.005	0.095		Legs fat mass	0.196	0.012	0.070
	Upper-body strength	-0.027	0.000	0.819		Upper-body strength	0.137	0.003	0.402
	Lower-body power	0.130	0.006	0.053		Lower-body power	0.086	0.003	0.408
	Moderate-to-vigorous PA	0.046	0.001	0.406		Moderate-to-vigorous PA	0.092	0.004	0.318
	Past bone-specific PA	0.063	0.003	0.199		**Past bone-specific PA**	**0.162**	**0.018**	**0.031**
FN aBMD (R^2=0.553) N = 98	Sex	0.168	0.014	0.064	Legs aBMD (R^2=0.818) N = 99	Sex	0.032	0.001	0.574
	Years from peak height velocity	0.154	0.004	0.355		**Years from peak height velocity**	**0.327**	**0.016**	**0.003**
	Time from treatment completion	**0.178**	**0.024**	**0.018**		Time from treatment completion	0.083	0.005	0.087
	Radiotherapy exposure	-0.072	0.004	0.301		Radiotherapy exposure	-0.051	0.002	0.250
	Legs lean mass	**0.426**	**0.022**	**0.021**		**Legs lean mass**	**0.400**	**0.019**	**0.001**
	Legs fat mass	0.220	0.015	0.055		Legs fat mass	0.096	0.003	0.202
	Upper-body strength	-0.049	0.000	0.775		Upper-body strength	0.110	0.002	0.316
	Lower-body power	0.125	0.005	0.256		Lower-body power	0.093	0.003	0.183
	Moderate-to-vigorous PA	0.120	0.006	0.218		Moderate-to-vigorous PA	0.062	0.002	0.277
	Past bone-specific PA	0.105	0.007	0.183		Past bone-specific PA	0.055	0.002	0.272
LS aBMD (R^2=0.605) N = 99	**Sex**	**0.182**	**0.017**	**0.031**	Arms aBMD (R^2=0.840) N = 98	Sex	-0.069	0.002	0.196
	Years from peak height velocity	0.248	0.010	0.105		**Years from peak height velocity**	**0.398**	**0.027**	**<0.001**
	Time from treatment completion	0.022	0.000	0.751		Time from treatment completion	-0.012	0.000	0.798
	Radiotherapy exposure	-0.079	0.005	0.222		Radiotherapy exposure	-0.001	0.000	0.983
	Trunk lean mass	**0.517**	**0.023**	**0.014**		**Arms lean mass**	**0.401**	**0.017**	**0.001**
	Trunk fat mass	0.150	0.007	0.163		**Arms fat mass**	**0.232**	**0.028**	**<0.001**
	Upper-body strength	-0.019	0.000	0.915		Upper-body strength	0.010	0.000	0.940
	Lower-body power	0.069	0.002	0.479		Lower-body power	0.088	0.003	0.158
	Moderate-to-vigorous PA	0.077	0.003	0.353		Moderate-to-vigorous PA	0.070	0.003	0.187
	Past bone-specific PA	-0.075	0.004	0.305		**Past bone-specific PA**	**0.097**	**0.006**	**0.039**

Standardized β coefficient, R^2 (Stein´s equation), Squared semipartial correlation and P value are provided (Boldface indicates $P<0.050$). Abbreviations: sr^2, squared semipartial correlation; aBMD, areal bone mineral density; TBLH, total body less head; FN, femoral neck; LS, lumbar spine; PA, physical activity.

Table 3. Multiple regressions models for Hip Structural Analysis and Trabecular Bone Score parameters.

	Predictors	β	sr^2	*P*		Predictors	β	sr^2	*P*
NN CSA (R^2=0.646) N = 98	Sex	0.051	0.001	0.524	NN SECT MOD (R^2=0.584) N = 98	Sex	0.005	0.000	0.952
	Years from peak height velocity	0.123	0.002	0.407		Years from peak height velocity	0.060	0.001	0.711
	Time from treatment completion	**0.135**	**0.014**	**0.043**		Time from treatment completion	0.077	0.004	0.282
	Radiotherapy exposure	0.007	0.000	0.905		Radiotherapy exposure	-0.012	0.000	0.858
	Legs lean mass	**0.628**	**0.049**	**<0.001**		**Legs lean mass**	**0.709**	**0.062**	**<0.001**
	Legs fat mass	0.101	0.003	0.317		Legs fat mass	0.009	0.000	0.936
	Upper-body strength	0.026	0.000	0.863		Upper-body strength	0.106	0.002	0.527
	Lower-body power	0.053	0.001	0.584		Lower-body power	-0.027	0.000	0.798
	Moderate-to-vigorous PA	0.114	0.006	0.189		Moderate-to-vigorous PA	0.094	0.004	0.317
	Past bone-specific PA	0.008	0.000	0.912		Past bone-specific PA	-0.046	0.001	0.544
NN CSMI (R^2=0.442) N = 98	Sex	-0.051	0.001	0.608	TBS (R^2=0.439) N = 99	**Sex**	**0.245**	**0.031**	**0.015**
	Years from peak height velocity	0.030	0.000	0.870		Years from peak height velocity	0.246	0.009	0.176
	Time from treatment completion	0.048	0.002	0.564		Time from treatment completion	0.101	0.007	0.231
	Radiotherapy exposure	0.008	0.000	0.914		Radiotherapy exposure	-0.085	0.006	0.272
	Legs lean mass	**0.757**	**0.071**	**<0.001**		**Trunk lean mass**	**0.775**	**0.051**	**0.002**
	Legs fat mass	-0.093	0.003	0.463		Trunk fat mass	-0.069	0.002	0.588
	Upper-body strength	0.110	0.002	0.568		**Upper-body strength**	**-0.443**	**0.023**	**0.036**
	Lower-body power	-0.081	0.002	0.509		Lower-body power	0.174	0.012	0.134
	Moderate-to-vigorous PA	0.089	0.003	0.413		Moderate-to-vigorous PA	-0.006	0.000	0.954
	Past bone-specific PA	-0.113	0.009	0.198		Past bone-specific PA	-0.040	0.001	0.648

Standardized β coefficient, R^2 (Stein´s equation), Squared semipartial correlation and P value are provided (Boldface indicates P<0.050). Abbreviations: sr^2, Squared semipartial correlation; aBMD, areal bone mineral density; NN CSA, narrow neck cross-sectional area (cm^2); NN CSMI, narrow neck cross-sectional moment of inertia (cm^4); NN SECT MOD, narrow neck section modulus (cm^3); TBS, trabecular bone score; PA, physical activity.

Discussion

Region-specific lean mass was the principal explanatory variable at most sites of the skeleton. Moreover, we found that years from PHV was a positive significant predictor only for aBMD at total body less head, legs and arms; and longer time from treatment completion was a positive significant predictor at femoral neck, total hip and narrow neck cross sectional area. This means that longer periods after treatment completion indicate better bone health. Finally, other factors such as sex (being female) and past bone-specific physical activity had a positive significant but small contribution to aBMD, HSA parameters and TBS.

Determinants of areal bone mineral density

Previous findings in healthy population with similar models of determinants explained 40% to 83% of the variance in bone mineral content [17]. Our results show that the strongest positive determinant was region-specific lean mass which is consistent with findings from previous studies in healthy children and adolescents [44] and, children with cancer during [45] and after oncological treatment [46,47]. This is explained mainly due to the Frost's mechanostat theory since inadequate lean mass acquisition impairs bone development [48]. In relation to the association of region-specific fat mass and aBMD parameters, our findings indicate negligible associations after accounting for other predictors in the model. The strong effect of other predictors such as years from PHV and sex are likely to moderate the relationship between fat mass and bone parameters [49]. However, contrary findings were found by Mostoufi-Moab et al. [50] in survivors of paediatric hematopoietic stem cell transplantation (aged 12-25 years). In their study, fat mass was inversely associated with abnormal trabecular architecture. Discrepancies between studies might be explained by the differences in the age of the participants, number of predictor variables as well as the paediatric cancer treatment received by the participants since both hematopoietic stem cell transplantation and total body irradiation are known to impair the normal fat-bone axis [51].

In the present analysis, we found that years from PHV had a positive association with aBMD at total body less head, legs and arms aBMD. In this regard, pre, peri and postpubertal periods are vital periods for bone development during normal growth [52] and even more critical after paediatric cancer diagnosis [46]. Time from treatment completion also had a positive association with femoral neck and total hip aBMD. This backs up that aBMD parameters improve with increasing time-off therapy after the exposure to oncological treatment [4].

Past bone-specific physical activity had a positive association only with total hip and arms aBMD. After adjusting for other covariates, the contribution of past bone-specific physical

activity does not seem noticeable, perhaps because of the strong relationship of region-specific lean mass. Additionally, depending on the osteogenic characteristics, the type of physical activity affects differently the skeletal development in this population [53-55]. In our study, 70% of the participants in the top quartile related to osteogenic stimulus calculated by past bone-specific physical activity reported football as one the sports practices along the life, while 40% reported basketball. Our findings are in line with previous research indicating that past bone-specific physical activity could have a significant, but weak contribution on specific sites of the skeleton in healthy adolescents [6]. The cause of this low bone mass is multifactorial and hence, finding the major contributors of aBMD, HSA parameters and TBS in young paediatric cancer survivors is of clinical relevance to target earlier recovery strategies.

Determinants of Hip Structural Analysis parameters and Trabecular Bone Score

Previous work in healthy population showed that HSA can provide more thorough geometrical evaluation at the hip site compared with aBMD parameters [56]. In agreement with Macdonald et al. [40], the results of our study highlight the association of region-specific lean mass and HSA parameters during childhood and adolescence. Previous findings in allogeneic hematopoietic stem cell transplantation survivors showed alterations in body composition following oncological treatment; increased fat mass while lean mass did the opposite [57]. These alterations partially explained the substantial deficits in trabecular volumetric bone mineral density and cortical geometry [58]. We did not find that region-specific fat mass was associated with any HSA parameters. However, the differences in the population characteristics, evaluation techniques and the region of interest make the studies incomparable. Of note, Mostoufi-Moab et al. [58] assessed bone, lean and fat mass at the 66% site of tibia using peripheral quantitative computed tomography. In our study, the time-off therapy was positively associated with the narrow neck cross sectional area after the exposure to oncological treatment like the femoral neck aBMD. This is consistent with findings of a previous review which identified that following completion of oncological therapy there is a substantial recovery in the femoral neck geometrical property [59]. Hence, the axial compression strength feature of the narrow femoral seems to improve specifically with time after therapy.

Similar to aBMD and HSA parameters, the strongest determinant for the TBS was region-specific lean mass which agrees with previous studies in healthy population [60]. However, they did not distinguish the site-specific relationship of lean mass which, in fact, was considered in the present study. Being female in this cohort had a positive association with bone texture acquisition at the lumbar spine, showing a diminished contribution once other factors (e.g.,

region-specific lean mass) were accounted. This aligns with a previous study in which TBS at baseline was significantly higher in females than males (TBS in males: 1.345±0.095; and females: 1.370±0.099) [36]. This shows the beneficial effects of time-off therapy on bone impairments caused by oncological treatment. However, the limited number of studies using TBS in young paediatric cancer survivors does not allow further comparisons, reflecting the novelty of this study. Our findings also indicate that upper-body strength had a weak negative association with TBS, in contrast with scientific literature in healthy children [61]. This surprising finding needs to be confirmed in this population.

One limitation of our study consisted of the cross-sectional approach and hence, it cannot be proved cause and effect between the determinants and bone outcomes. To the best of our knowledge, this is the first study conducted in young paediatric cancer survivors examining the determinants of aBMD, HSA parameters and TBS. Many predictors have been taken into account adjusting their effects by each other. Additionally, this study specifically uses region-specific lean mass as predictor because of the site-specific adaptations of the skeleton during growth [62].

Conclusion

Region-specific lean mass was consistently the most important positive determinant of all bone parameters. Years from PHV and time from treatment completion were also found to be important positive determinants for the aBMD and HSA parameters. Randomised clinical trials focusing on bone outcomes of young paediatric cancer survivors should focus on improving region-specific lean mass due to the site-specific adaptations of the skeleton to external loading and unloading following cancer treatment. Interventional studies after paediatric cancer and its treatment should meet the clinical need of including resistance training to increase lean mass before including weight-bearing exercises with a view to improving bone health.

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Supplementary material

Table S1. STROBE Statement-Checklist of items that should be included in reports of *cross-sectional studies*.

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	99
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	99
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	100-101
Objectives	3	State specific objectives, including any prespecified hypotheses	100-101
Methods			
Study design	4	Present key elements of study design early in the paper	101
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	101
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	101-102
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	102-104
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	101-104
Bias	9	Describe any efforts to address potential sources of bias	104-105
Study size	10	Explain how the study size was arrived at	101-105
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	104-105
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	104-105
		(*b*) Describe any methods used to examine subgroups and interactions	104-105
		(*c*) Explain how missing data were addressed	104-105

		(*d*) If applicable, describe analytical methods taking account of sampling strategy	104-105
		(*e*) Describe any sensitivity analyses	104-105
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Not applicable
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1 and Table S2
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1-3
Outcome data	15*	Report numbers of outcome events or summary measures	Tables 1-3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 2 and 3
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	105-106
Discussion			
Key results	18	Summarise key results with reference to study objectives	110
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	112
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	110-112
Generalisability	21	Discuss the generalisability (external validity) of the study results	112
Other information			

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

Note: An explanation and elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Table S2. Distribution of cancer types of participants included in this study.

	Total		Females		Males	
	%	N	%	N	%	N
Acute lymphoblastic leukemia	38.8	45	36.7	18	40.3	27
Lymphoma	12.1	14	12.2	6	11.9	8
Central nervous system	9.5	11	10.2	5	9.0	6
Renal tumor	7.8	9	4.1	2	10.5	7
Neuroblastoma	6.9	8	12.2	6	3.0	2
Malignant bone tumor	6.9	8	8.2	4	6.0	4
Histiocytosis	5.2	6	6.1	3	4.5	3
Soft tissue and other extraosseous sarcomas	4.3	5	0.0	0	7.5	5
Retinoblastoma	3.5	4	4.1	2	3.0	2
Hepatic tumor	2.6	3	4.1	2	1.5	1
Other malignant epithelial neoplasms	1.7	2	2.0	1	1.5	1
Unspecified malignant neoplasms	0.9	1	0.0	0	1.5	1

Table S3. Partial correlation coefficients between bone parameters, calcium intake and vitamin D deficiency in young paediatric cancer survivors.

Bone parameters	Calcium intake			Vitamin D status		
	r	*P*	N	r	*P*	N
Total body less head aBMD (g/cm^2)	-0.068	0.482	107	-0.097	0.315	107
Femoral neck aBMD (g/cm^2)	-0.026	0.786	106	-0.105	0.280	106
Lumbar spine aBMD (g/cm^2)	0.086	0.376	107	-0.123	0.201	107
Total Hip aBMD (g/cm^2)	-0.100	0.305	106	-0.122	0.209	106
Legs aBMD (g/cm^2)	-0.122	0.207	107	-0.077	0.427	107
Arms aBMD (g/cm^2)	0.043	0.659	106	-0.042	0.669	106
Narrow neck cross-sectional area (cm^2)	-0.080	0.408	106	-0.097	0.315	106
Narrow neck cross-sectional moment of inertia (cm^4)	-0.125	0.198	106	-0.030	0.755	106
Narrow neck section modulus (cm^3)	-0.119	0.219	106	-0.073	0.454	106
Trabecular Bone Score	0.094	0.329	107	0.031	0.748	107

Analyses were adjusted by sex and years from peak height velocity. Calcium intake in milligrams and Vitamin D status were estimated by validated food-frequency questionnaires. Vitamin D status was based on three questions regarding sun exposure during the last year (yes/no), use of tanning booth (yes/no) and the number of glasses of milk per day (two or more glasses were considered as yes and less than two glasses were considered as no). Using the threshold of two out of three negative responses for these habits proposed by we identified participants with vitamin D status. No significant correlations were found when $p>0.05$. Abbreviations: aBMD, areal bone mineral density (g/cm^2).

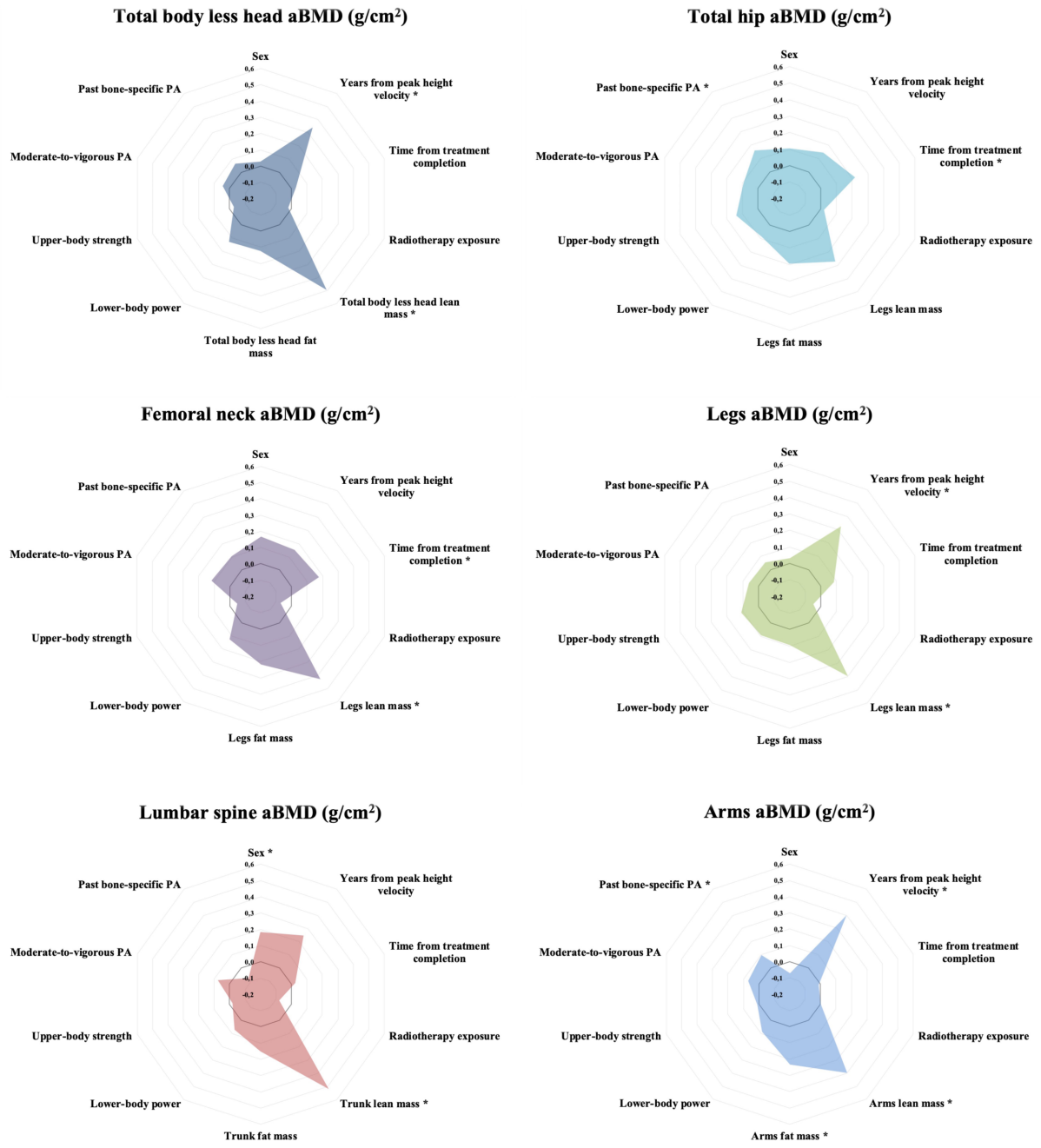

Figure S1. Radar plots visualisation of the multiple regression model for areal bone mineral density parameters (total body less head, femoral neck, lumbar spine, total hip, legs and arms) and the standardised β coefficient of each predictor. Abbreviations: aBMD, areal bone mineral density; PA, physical activity.

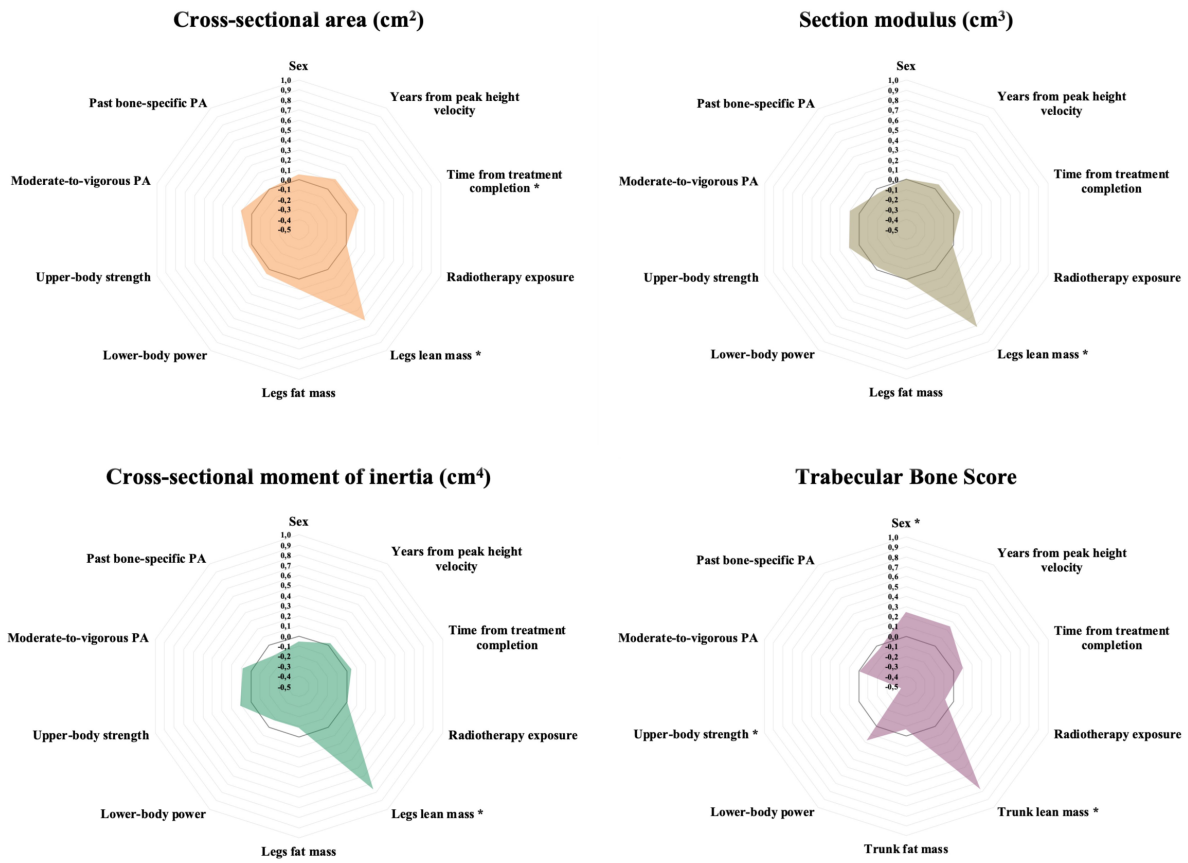

Figure S2. Radar plots visualisation of the multiple regression model for Hip Structural Analysis and Trabecular Bone Score parameters and the standardised β coefficient of each predictor. Abbreviations: PA, physical activity.

Chapter 6. Lean mass attenuates negative associations of watching television with bone parameters in young paediatric cancer survivors

Abstract

Objective. To investigate the role of lean mass in the associations of TV watching time with bone parameters and to examine whether high lean mass attenuates the negative impact of watching TV more than one hour per day on bone parameters.

Methods. This cross-sectional study comprised 116 young paediatric cancer survivors. DXA was used to obtain total body and regional aBMD (g/cm^2), and lean mass (kg) outcomes. HSA was performed at the narrowest point of the femoral neck. TBS was obtained in the lumbar spine. TV watching time was obtained using the "Youth Activity Profile" questionnaire.

Results. Multiple linear regression models showed negative associations of watching television more than one hour with bone parameters in peri/post pubertal survivors (β = -0.275 to -0.560, $P < .001$ to .047). However, most associations attenuated to the null after region-specific lean mass was accounted. Those survivors watching TV more than one hour per day and with high lean mass presented higher bone parameter Z-score than those with low lean mass.

Conclusion. These findings underline the necessity of identifying strategies that promote musculoskeletal development while reducing TV watching time in young paediatric cancer survivors to maximize bone regeneration.

Introduction

At present, the 5-year survival rate for all paediatric cancers is 85% for children and 82% for adolescents [1]. However, up to two-thirds of young paediatric cancer survivors may present low areal bone mineral density (aBMD) [2]. Decreased bone formation and increased bone resorption lead to skeletal demineralization due to the disease itself and certain oncological cancer treatment [3]. Moreover, paediatric cancer occurs during a critical phase for bone acquisition and strengthening, providing a unique window of opportunity to reclaim bone mass and density since up to 95% of the adult bone mass may be accrued by the end of adolescence [4].

SB contribute to an increased risk of comorbidities, chronic diseases and low aBMD during childhood and adolescence [5]. TV watching is one of these SB highly prevalent among survivors (3.24 ± 1.68 hours per day) [6] and therefore, its relationship with bone health could presumably be negative. To date, the dearth of studies in this area shows inconsistent findings with an insufficiently robust control necessary to characterize bone parameters relative to age, sex, race, somatic maturity and body size [7-9]. Thus, the association of a prevalent SB such as TV watching with bone parameters have not been comprehensively unveiled in this population.

Previous studies have demonstrated that lean mass is an important determinant of bone health in young paediatric cancer survivors [10,11]. Results observed in individuals who have undergone allogeneic hematopoietic stem cell transplantation (aged 5-26 years old) showed a strong relationship between low lean mass and bone volumetric fraction, trabecular volumetric BMD and cortical geometry deficits, compared with young healthy population [12-14]. Frost's mechanostat theory could explain this relationship because larger muscles apply increased forces on the bones to which they are connected [15]. Therefore, investigating the protective role of lean mass in the association of TV watching time with bone parameters assessed with a variety of techniques among young paediatric cancer survivors has not been studied in depth nor in this population.

The aims of this study in young paediatric cancer survivors were: (1) to investigate the role of lean mass in the association of TV watching time with bone parameters; and (2) to examine whether having high lean mass attenuates the negative association of watching TV more than one hour per day with bone parameters Z-score.

Methods

Study Design and Participants

The present cross-sectional analysis refers to baseline data and includes 116 young paediatric cancer survivors of the iBoneFIT project, a randomized controlled trial (https://www.isrctn.com/ISRCTN61195625) whose protocol has been published elsewhere [16]. Inclusion criteria were aged from 6 to 18 years, not currently receiving treatments for cancer, diagnosed at least one year prior to enrolment and previous exposure to radiotherapy and/or chemotherapy. Data collection occurred in two waves due to COVID-19 restrictions: 1) October 2020 to February 2021; and 2) December 2021 to March 2022. The Ethics Committee on Human Research of the Regional Government of Andalusia granted approval to the iBoneFIT project in December 2019 (Reference: 4500). The project adhered to the ethical principles outlined in the Declaration of Helsinki, with its revised version from 2013 serving as a guide. The STROBE [17] checklist was followed in this study (**Table S1**). Despite recruiting a total of 116 individuals, the sample size for various variables was slightly reduced due to missing data (i.e., inability to complete certain tests, felt uncomfortable having their bodies scanned by DXA, or were unwilling to cooperate on evaluations).

Anthropometry and Somatic Maturity

We assessed body mass (kg) with an electronic scale (SECA 861, Hamburg, Germany) with an accuracy of 100 g. Stature (cm) was measured using a precision stadiometer (SECA 225, Hamburg, Germany) to the nearest 0.1 cm. Body mass index was calculated as body mass (kg)/height (m^2). Additionally, age- and sex-specific body mass index Z-score and categories were calculated using international reference data for paediatric population [18]. Somatic maturity was assessed using the prediction of years from peak height velocity (PHV) using validated algorithms for boys and girls [19].

Clinical Data and Calcium

Medical record abstraction was used to ascertain diagnosis, time from treatment completion to baseline data collection and treatment exposures (chemotherapy and/or radiotherapy and/or surgery). Time from treatment completion was treated as a continuous variable. We computed a dichotomous variable based on the type of treatment (radiotherapy; yes/no) and used as a covariate because radiotherapy is a strong risk factor for persistent low aBMD in young paediatric cancer survivors [20]. Finally, daily calcium (in milligrams) intake was estimated by a validated specific food-frequency questionnaire [21].

Television Watching Time

TV watching time was obtained using the seven-days recall Spanish adaptation of the YAP questionnaire which was cross-translated (available at: https://profith.ugr.es/yap?lang=en). This questionnaire asks how much time survivors were watching TV and there were five possible answers: i) I did not watch TV at all; ii) I daily watched TV for less than one hour; iii) I daily watched TV between one and two hours; iv) I daily watched TV for more than two hours and less than three hours; and v) I daily watched TV for more than three hours. Given the low prevalence of survivors in the last three categories, these were grouped into one, so the variable was recoded as follows: 0, <1 hour and >1 hour. The YAP questionnaire was created at the Iowa State University and validated in children [22]. This has been previously calibrated against accelerometer-determined SB and physical activity, and cross-validated in a different cohort against accelerometer estimates being feasible and reliable [23].

Dual-energy X-ray Absorptiometry (DXA)

All survivors underwent assessment using a unique DXA scanner (Hologic Series Discovery QDR located in Bedford, Massachusetts, USA), and the data were processed using APEX software (version 4.0.2). The analyses were conducted in accordance with the guidelines outlined by the International Society of Clinical Densitometry [24]. To ensure accuracy, the device was calibrated daily using a lumbar spine phantom. Three scans, encompassing the total body (excluding the head), right hip, and lumbar spine, were conducted to determine the aBMD (g/cm^2) of the total body (excluding the head), total hip, femoral neck, and lumbar spine (mean of L1–L4). The total body (excluding the head) values were favoured over total body measurements following recommendations for paediatric population [24]. These three scans also provided data on lean mass, calculated as body mass minus the sum of fat mass and bone mass, for the total body (excluding the head), hip, and trunk. It is important to note that the coefficient of variation for DXA scans in the paediatric population varies between 1.0% and 2.9%, depending on the specific region being assessed [25].

Hip Structural Analysis (HSA)

The DXA scan procedure was conducted at the narrowest point of the femoral neck. Using the distribution of bone mineral mass, the software examined the structural characteristics along a line of pixels running across the bone axis [26]. The resulting parameters included: (1) narrow neck (NN) cross-sectional area (cm^2), which is the bone surface area in the cross-section after excluding soft tissue and trabecular space, provides an index of axial compression strength; (2) NN cross-sectional moment of inertia (cm^4), which is the index of structural rigidity and; (3)

NN section modulus (cm^3), which is the bending strength indicator for maximum bending stress in the direction of the image plane. The coefficient of variation for the HSA varies between 2.4% and 6.4%, depending on the specific parameter being examined variable [27].

Trabecular Bone Score (TBS)

The iNsight Software (Medimaps, research version 3.0, Pessac, France) offers an indirect assessment of the textural characteristics of trabecular microarchitecture in the lumbar spine. This technology, which relies on DXA, has demonstrated a significant capability to predict fracture risk, making it a recognized indicator of bone quality [28]. TBS assesses the variability in grey-level pixel values in aBMD scans, which implies reduced trabecular connectivity and is determined by experimental variograms of the projected DXA image [29]. The coefficient of variation for TBS falls within the range of 1.1% to 1.9% for aBMD measurements in the lumbar spine aBMD [30]. While TBS has predominantly been utilized in the adult population [31], its application has expanded to encompass the paediatric population in recent years [32].

Statistical Analyses

The normal distribution of the continuous variables was checked and verified using Kolmogorov-Smirnov test, skewness and kurtosis values, visual check of histograms, Q-Q and box plots. Descriptive data were reported as mean and standard deviation (for continuous variables) or number and percentages (for categorical variables).

Multiple linear regression analyses were used to assess the relationships of watching TV less than one hour and more than one hour (compared to not watching TV) with bone parameters by somatic maturity groups (prepubertal, < -1 year from PHV and; peri/post-pubertal, > -1 year from PHV), in accordance with Faigenbaum et al. [33]. The regression models were built in four steps: Model 0, shows crude associations; Model 1, adjusted for sex; Model 2, included covariates in model 1 plus time from treatment completion and baseline evaluation (years) and radiotherapy exposure (yes/no); Model 3, included covariates in model 2 plus region-specific lean mass (total body [less head], legs or trunk); and Model 4 included covariates in model 3 plus calcium intake (mg). Region-specific lean mass was used for regional bone parameters instead of total lean mass because of the specific adaptations of the skeleton region [34]. Therefore, the chosen region-specific for total hip, femoral neck, narrow neck cross-sectional area, cross-sectional moment of inertia and section modulus was legs lean mass and for lumbar spine and TBS was trunk lean mass. β coefficients are presented standardized and R2 adjusted. The selection of the covariates used was based on their

relationship with bone parameters [33-35]. Additionally, analysis of covariance (ANCOVA) was used to examine differences in bone parameters Z-score (outcome variables) by groups of lean mass (low/high; fixed factor) in those survivors who watched TV more than one hour per day (N = 47). Lean mass groups were created by obtaining maturity- and sex-specific percentiles of region-specific lean mass, and a dichotomous variable was created to classify survivors in the 'low lean mass' group (< percentile 50) or 'high lean mass' group (> percentile 50). All bone parameters were standardized (Z-score) according to sex and years from PHV. Covariates included the time from treatment completion (years) and radiotherapy exposure (yes/no). All calculations were performed using the Statistical Package for the Social Sciences v.24 (SPSS Inc) and the statistical software R version 4.0.3 (R Foundation for Statistical Computing). Values of $P < .05$ were considered statistically significant.

Results

Table 1 shows data on descriptive characteristics of the young paediatric cancer survivors by somatic maturity groups. The average age of the total sample was 12.1 (3.3) years and 42.2% were female. On average, 81.6% of survivors reported watching TV. Regarding bone health, the average of total body (less head) aBMD Z-score was -0.2 (1.4); total hip aBMD Z-score was 0.1 (1.3); femoral neck aBMD Z-score was -0.2 (1.4); lumbar spine aBMD Z-score was -0.1 (1.3). **Table 2** presents cancer types of all survivors and by somatic maturity groups. Most survivors were previously diagnosed with acute lymphoblastic leukaemia (38.8%).

Table 3 shows multiple linear regression analyses of watching TV more than one hour (compared to not watching TV) with bone parameters according to somatic maturity and controlling for different sets of covariates. No significant associations were found in prepubertal survivors across all models (all β coefficient < 0.346, $P > .05$). In peri/post-pubertal survivors, several negative associations were found. After adjusting for sex (model 1), TV watching time was negatively associated with all bone parameters (β coefficient = -0.360 to -0.560, $P < .001$ to .028), except for narrow neck cross-sectional moment of inertia. After adjusting for time from treatment completion and radiotherapy exposure (model 2), all negative associations remained significant, except for narrow neck section modulus. However, after adjusting for region-specific lean mass (model 3), most negative associations attenuated to the null. In additional analyses (model 4), calcium intake was added as a covariate and results did not differ from those shown in model 3 (**Table S2**). Multiple linear regression analyses of watching TV less than one hour (compared to not watching TV) with bone parameters are presented in **Table S3**.

Figures 1 and **2** present differences in bone parameters Z-score according to maturity- and sex-specific lean mass levels (low/high) in survivors who watched TV more than one hour. Survivors with high lean mass showed significantly higher aBMD Z-score at total body (less head), total hip, femoral neck and lumbar spine compared to those with low lean mass (**Figure 1**). There were also significant differences in bone parameters Z-score using hip geometry estimates, but the differences using TBS did not reach statistical significance (**Figure 2**).

Table 1. Descriptive characteristics of the survivors included in the study.

	Total	N	Prepubertal	N	Peri/post-pubertal	N
Sex (female/male, %)	42.2/57.8	116	37.9/62.1	58	46.5/53.5	58
Age (years)	12.1 (3.3)	116	9.3 (1.8)	58	14.9 (1.7)	58
Body mass (kg)	46.6 (18.0)	116	34.1 (9.3)	58	59.1 (16)	58
Stature (cm)	147.5 (17.1)	116	133.4 (10.9)	58	161.6 (8)	58
Body mass index Z-score	0.9 (1.1)	116	1.0 (1.1)	58	0.8 (1.2)	58
Body mass index (categories)						
Underweight	3.5	4	3.5	2	3.4	2
Normoweight	61.2	71	56.9	33	65.5	38
Overweight	20.7	24	22.4	13	19.0	11
Obese	14.6	17	17.2	10	12.1	7
Years from peak height velocity	-0.8 (2.7)	116	-3.1 (1.2)	58	1.6 (1.5)	58
Time from treatment completion (years)	5.0 (3.8)	113	3.4 (2.6)	56	6.6 (4.1)	57
Radiotherapy exposure (yes/no, %)	27.6/72.4	116	25.9/74.1	58	29.3/70.7	58
Calcium intake (mg/day)	785.5 (437.2)	116	845.7 (496.9)	58	725.2 (362.3)	58
TV watching time (%)						
0 h	18.4	21	8.8	5	28.1	16
<1h	38.6	44	43.8	25	33.3	19
≥1h	43.0	49	47.4	27	38.6	22
Lean mass (kg)						
Total body less head	25.7 (10.4)	116	18.0 (5.0)	58	33.5 (8.4)	58
Legs	4.6 (2.0)	116	3.2 (1.0)	58	6.0 (1.6)	58
Trunk	14.3 (5.6)	116	10.1 (2.6)	58	18.6 (4.4)	58
aBMD (g/cm^2)						
Total body less head	0.791 (0.159)	116	0.671 (0.091)	58	0.911 (0.115)	58
Total hip	0.823 (0.169)	115	0.718 (0.104)	58	0.929 (0.156)	57
Femoral neck	0.732 (0.152)	115	0.644 (0.095)	58	0.822 (0.147)	57
Lumbar spine	0.731 (0.187)	116	0.599 (0.087)	58	0.862 (0.167)	58
Hip structural analysis						
Cross-sectional area (cm^2)	2.203 (0.677)	115	1.755 (0.404)	58	2.658 (0.589)	57
Cross-sectional moment of inertia (cm^4)	1.378 (0.861)	115	0.912 (0.691)	58	1.852 (0.754)	57
Section modulus (cm^3)	0.871 (0.416)	115	0.614 (0.277)	58	1.132 (0.369)	57
Trabecular bone score	1.318 (0.103)	116	1.256 (0.070)	58	1.381 (0.091)	58

Data are presented as mean (standard deviation) or as frequencies (percentages), as indicated. Areal bone mineral density (aBMD) Z-score parameters are presented using international reference data from the Bone Mineral Density in Childhood Study. Abbreviations: aBMD, areal bone mineral density.

Table 2. Distribution of cancer types of survivors included in this study.

	Total		Prepubertal		Peri/Post-pubertal	
	%	N	%	N	%	N
Acute lymphoblastic leukaemia	38.8	45	41.4	24	36.2	21
Lymphoma	12.1	14	13.8	8	10.3	6
Central nervous system	9.5	11	5.2	3	13.8	8
Renal tumour	7.8	9	8.6	5	6.9	4
Neuroblastoma	6.9	8	12.1	7	1.7	1
Malignant bone tumour	6.9	8	3.5	2	10.3	6
Histiocytosis	5.2	6	5.2	3	5.2	3
Soft tissue and other extraosseous sarcomas	4.3	5	5.2	3	3.5	2
Retinoblastoma	3.4	4	1.7	1	5.2	3
Hepatic tumor	2.6	3	3.5	2	1.7	1
Other malignant epithelial neoplasms	1.7	2	0	0	3.5	2
Unknown	0.9	1	0	0	1.7	1

Table 3. Multiple lineal regressions for the associations of watching television more than one hour, N=49 (compared to not watching television, N=21) and bone parameters in prepubertal and peri/post-pubertal young paediatric cancer survivors.

		Pre-pubertal					Peri/post-pubertal				
		B	95% CI	A. R^2	f^2	*P*	B	95% CI	A. R^2	f^2	*P*
Total body less head aBMD (g/cm^2)	Model 1	-0.223	(-0.709, 0.263)	0.036	0.037	.361	-0.473	(-0.796, -0.151)	0.098	0.109	**.005**
	Model 2	-0.240	(-0.726, 0.245)	0.056	0.059	.324	-0.405	(-0.741, -0.069)	0.100	0.111	**.019**
	Model 3	-0.074	(-0.310, 0.161)	0.781	3.566	.528	-0.218	(-0.463, 0.027)	0.543	1.188	.080
Total hip aBMD (g/cm^2)	Model 1	-0.026	(-0.513, 0.461)	0.032	0.033	.915	-0.441	(-0.770, -0.112)	0.073	0.079	**.010**
	Model 2	-0.011	(-0.491, 0.469)	0.076	0.082	.962	-0.352	(-0.687, -0.017)	0.111	0.125	**.040**
	Model 3	0.093	(-0.280, 0.466)	0.448	0.812	.619	-0.225	(-0.516, 0.066)	0.355	0.550	.127
Femoral neck aBMD (g/cm^2)	Model 1	0.111	(-0.389, 0.611)	-0.021	-0.021	.657	-0.560	(-0.873, -0.248)	0.162	0.193	**.001**
	Model 2	0.091	(-0.401, 0.583)	0.031	0.032	.711	-0.453	(-0.766, -0.141)	0.226	0.292	**.005**
	Model 3	0.192	(-0.204, 0.588)	0.377	0.605	.334	-0.335	(-0.607, -0.063)	0.439	0.783	**.017**
Lumbar spine aBMD (g/cm^2)	Model 1	0.004	(-0.504, 0.513)	-0.057	-0.054	.987	-0.401	(-0.712, -0.090)	0.161	0.192	**.012**
	Model 2	0.006	(-0.513, 0.524)	-0.077	-0.071	.982	-0.343	(-0.668, -0.018)	0.156	0.185	**.039**
	Model 3	0.088	(-0.411, 0.587)	0.021	0.021	.724	-0.129	(-0.384, 0.127)	0.517	1.070	.317
Cross-sectional area (cm^2)	Model 1	0.092	(-0.389, 0.573)	0.056	0.059	.703	-0.454	(-0.775, -0.133)	0.115	0.130	**.006**
	Model 2	0.089	(-0.400, 0.578)	0.041	0.043	.716	-0.375	(-0.705, -0.044)	0.134	0.155	**.027**
	Model 3	0.170	(-0.264, 0.603)	0.254	0.340	.435	-0.203	(-0.434, 0.027)	0.596	1.475	.083
Cross-sectional moment of inertia (cm^4)	Model 1	0.026	(-0.461, 0.513)	0.031	0.032	.914	-0.235	(-0.550, 0.081)	0.146	0.171	.141
	Model 2	0.015	(-0.486, 0.515)	-0.004	-0.004	.953	-0.196	(-0.528, 0.137)	0.126	0.144	.243
	Model 3	0.037	(-0.468, 0.541)	-0.008	-0.008	.885	0.001	(-0.183, 0.186)	0.741	2.861	.989
Section modulus (cm^3)	Model 1	0.049	(-0.433, 0.531)	0.051	0.054	.840	-0.360	(-0.679, -0.041)	0.125	0.143	**.028**
	Model 2	0.033	(-0.462, 0.528)	0.019	0.019	.894	-0.304	(-0.638, 0.030)	0.116	0.131	.073
	Model 3	0.078	(-0.405, 0.562)	0.072	0.078	.747	-0.106	(-0.291, 0.079)	0.741	2.861	.255
Trabecular bone score	Model 1	0.346	(-0.151, 0.843)	-0.010	-0.010	.168	-0.472	(-0.765, -0.179)	0.257	0.346	**.002**
	Model 2	0.338	(-0.133, 0.809)	0.110	0.124	.155	-0.441	(-0.748, -0.133)	0.246	0.326	**.006**
	Model 3	0.316	(-0.162, 0.795)	0.100	0.111	.190	-0.275	(-0.546, -0.004)	0.456	0.838	**.047**

Multiple linear regression analyses with several models of adjustment were performed as follows: model 1 (adjusted for sex), model 2 (adjusted for sex, time from treatment completion to baseline evaluation [years] and radiotherapy exposure [yes/no]) and model 3 (adjusted for sex, time from treatment completion to baseline evaluation [years], radiotherapy exposure [yes/no] and region-specific lean mass [g]). Region-specific for total hip, narrow neck cross-sectional area, cross-sectional moment of inertia and section modulus was legs lean mass and for lumbar spine and Trabecular Bone Score was trunk lean mass. Standardized β coefficient, adjusted R^2 and *P* value < .05 are provided in bold. Abbreviations: aBMD, areal bone mineral density (g/cm^2); CI, Confidence interval; TV, television.

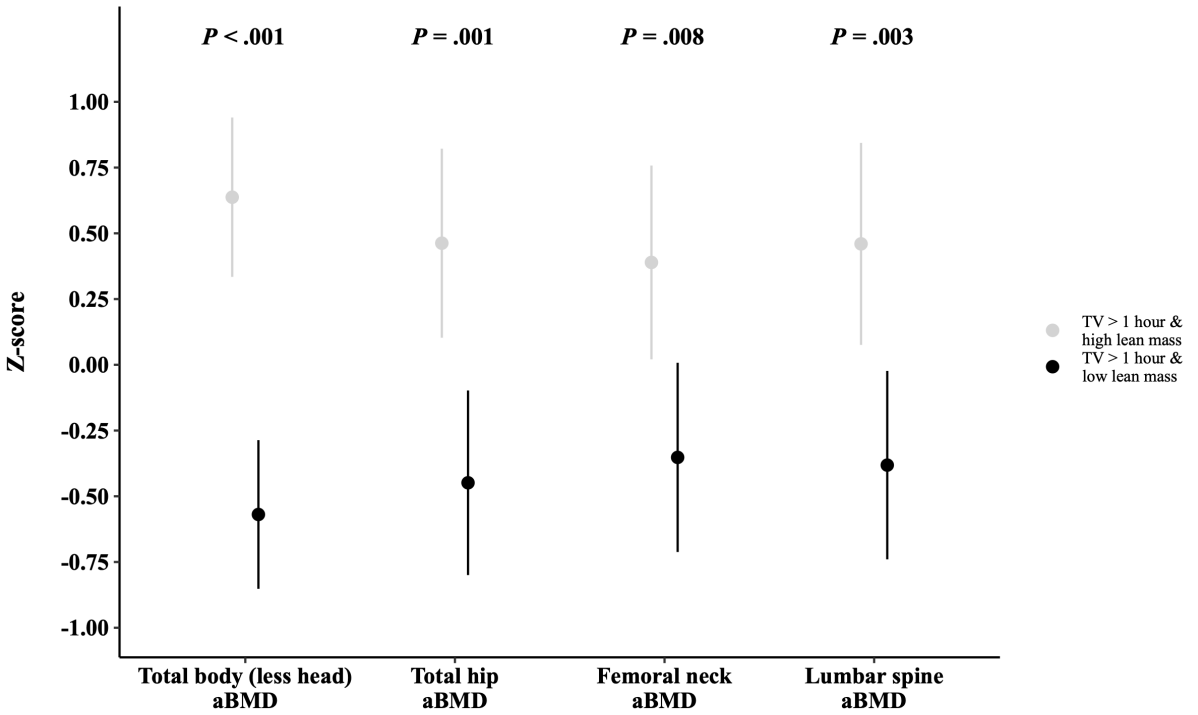

Figure 1. Differences in Z-score bone parameters by maturity- and sex-specific lean mass groups (low/high) using percentile 50 as threshold for those participants watching TV more than one hour per day (N = 47). Region-specific for total hip was legs lean mass and for lumbar spine was trunk lean mass. Data are presented as adjusted means and 95% confidence intervals. Analysis of covariance was used to compare differences between the lean groups and the analyses were adjusted for time from treatment completion to baseline evaluation (years) and radiotherapy exposure (yes/no). Significant differences are in bold (adjusted P value < .05). Abbreviations: aBMD, areal bone mineral density; TV, television.

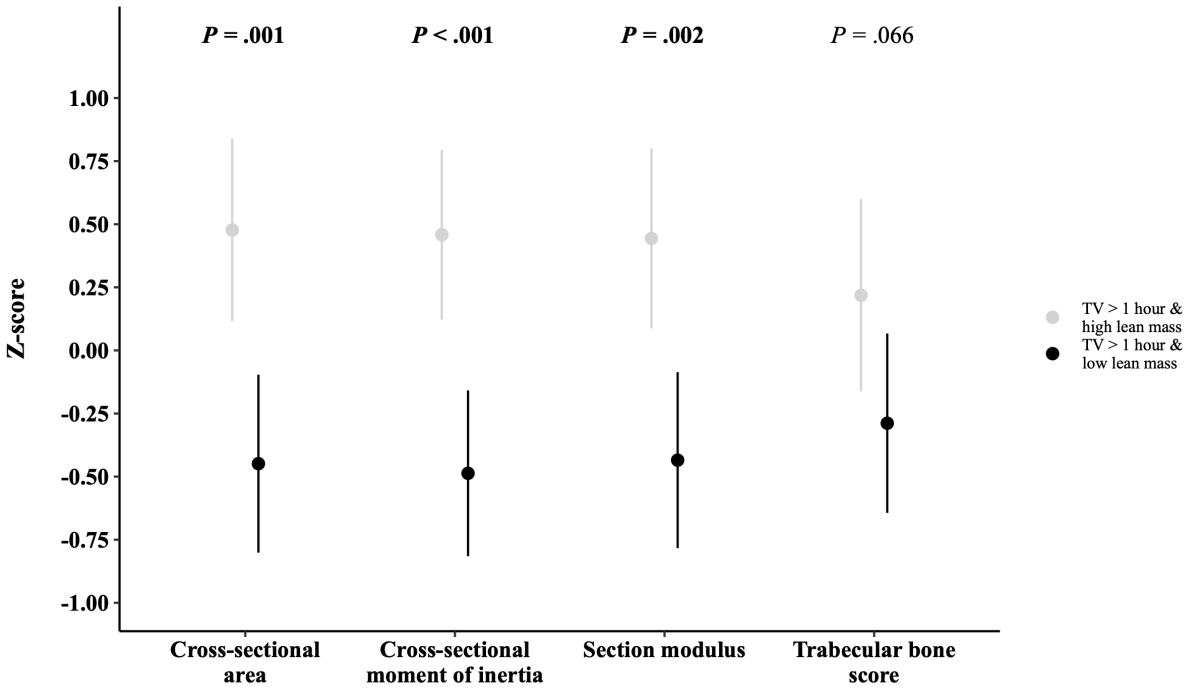

Figure 2. Differences in Z-score bone parameters by maturity- and sex-specific lean mass groups (low/high) using percentile 50 as threshold for those participants watching TV more than one hour per day (N = 47). Region-specific for total hip was legs lean mass and for lumbar spine was trunk lean mass. Data are presented as adjusted means and 95% confidence intervals. Analysis of covariance was used was used to compare differences between the lean groups and the analyses were adjusted for time from treatment completion to baseline evaluation (years) and radiotherapy exposure (yes/no). Significant differences are in bold (adjusted P value < .05). Abbreviations: TV, television.

Discussion

This observational study showed that TV watching time was negatively associated with most bone parameters in peri/post-pubertal survivors, but this association was dependent on lean mass. Importantly, those survivors watching TV more than one hour per day and with high lean mass presented higher bone parameters Z-score than those with low lean mass. These findings highlight the importance of promoting musculoskeletal development while reducing TV watching time to maximize bone regeneration after paediatric cancer.

Prolonged SB, such as TV watching time, have been proposed as a determinant factor for bone acquisition during growth [5]. The reasons why SB may limit aBMD during growth rely on the lack of mechanical forces as described by the Frost's mechanostat theory [15], which are key in the bone formation-resorption cellular activity a phenomenon previously. Prolonged TV watching time sitting or lying may reduce bone mass by augmenting bone resorption, without concomitant changes in bone formation [35]. In comparison with other sedentary activities, watching TV is characterized by spending a lot of time in the same position. As a result, prolonged time and situations without mechanical loading are likely to be detrimental for bone health [35].

In this study, the associations of TV watching time with bone parameters were found only in peri-post/pubertal paediatric cancer survivors. This could be explained because the peri-post/pubertal survivors are likely to have been exposed to this behavior for a longer time [35]. This is in line with previous work in children and adolescents during and following oncological treatment that showed less capacity to recover from fractures in the older ones due to insufficient residual growth potential [10]. Previous research in paediatric cancer survivors aged nine to 18 years old showed a higher risk of having reduced whole body aBMD (including head) in those watching TV more than two hours per day, after controlling for sex, age, ethnicity and pubertal stage (mean pubertal stage around their PHV) [7]. Likewise, Gunes et al. [8], indicated that TV watching time was negatively associated with aBMD at lumbar spine (L2-L4) in children completing treatment for acute lymphoblastic leukemia. However, their analyses were not controlled for any covariates such as lean mass nor somatic maturity despite the importance of lean mass [10], and the survivors' age range (3.4 to 17.5 years old). In contrast, Kelly et al. [9] did not find significant associations of TV watching time with whole body aBMD (including head) after controlling for age, ethnicity, height, weight and total body bone area in children with acute lymphoblastic leukemia during and following completion of treatment (aged 3 to 18 years old). In this study, most significant associations of TV watching time with bone parameters attenuated to the null once region-specific lean mass was controlled in the

models [36]. Surprisingly, none of the previous-mentioned studies accounted for lean mass despite being one of the strongest predictors of bone parameters during growth [10], which hampers comparisons in this regard [36]. Additionally, differences in bone parameters Z-score were investigated according to maturity- and sex-specific lean mass groups (low/high) in survivors watching TV more than one hour per day. Those with high lean mass presented significantly higher bone parameters Z-score than survivors with low lean mass. In line with the study of Polgreen et al. [7], these findings show the protective role of lean mass for bone health when a prolonged SB such as TV watching time is prevalent. These findings are of clinical interest since this population is at risk of having low aBMD [37].

Some limitations of this study need to be acknowledged. First, the cross-sectional design does not allow to determine the causality of the findings and therefore, longitudinal studies are needed to confirm the negative effect of TV watching time on bone health. However, to the best of our knowledge, preserved bone health has not been demonstrated to either increase or decrease TV watching time. Second, although analyses were controlled for relevant covariates, it cannot be certain that other unmeasured variables have not influenced these observations. Third, the seven-days recall Youth Activity Profile, which evaluates TV watching exposure, does not account for the multiple streaming platforms and hence, some participants might have not taken into consideration TV watching time across multiple streaming platforms.

Conclusions

This study indicated that TV watching time was negatively associated with most bone parameters in peri/post-pubertal survivors, but this association was dependent on lean mass. Noteworthy, survivors watching TV more than one hour per day and with high lean mass presented higher bone parameters Z-score than those with low lean mass. These findings underline the need of improving musculoskeletal development while reducing TV watching time after paediatric cancer.

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Supplementary material

Table S1. STROBE Statement-Checklist of items that should be included in reports of *cross-sectional studies.*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	126
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	126
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	126
Objectives	3	State specific objectives, including any prespecified hypotheses	127
Methods			
Study design	4	Present key elements of study design early in the paper	127-128
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	127-128
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	127-128
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	128-130
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	127-130
Bias	9	Describe any efforts to address potential sources of bias	130-131
Study size	10	Explain how the study size was arrived at	130-131
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	130-131
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	130-131
		(*b*) Describe any methods used to examine subgroups and interactions	130-131
		(*c*) Explain how missing data were addressed	130-131

		(*d*) If applicable, describe analytical methods taking account of sampling strategy	130-131
		(*e*) Describe any sensitivity analyses	130-131
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	No applicable
		(b) Give reasons for non-participation at each stage	No applicable
		(c) Consider use of a flow diagram	No applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1-2
		(b) Indicate number of participants with missing data for each variable of interest	Table 1-2
Outcome data	15*	Report numbers of outcome events or summary measures	Table 3, Figures 1-2 and Tables S2-3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3 and Figures 1-2
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	131-132
Discussion			
Key results	18	Summarise key results with reference to study objectives	138
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	139
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	138-139
Generalisability	21	Discuss the generalisability (external validity) of the study results	139

Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Table S2. Multiple lineal regressions for the associations of watching television more than one hour, N=49 (compared to not watching television, N=21) and bone parameters in prepubertal and peri/post-pubertal young paediatric cancer survivors.

		Pre-pubertal					Peri/post-pubertal				
		B	95% CI	A. R^2	f^2	*P*	B	95% CI	A. R^2	f^2	*P*
Total body less head aBMD (g/cm^2)	Model 4	-0.057	(-0.291, 0.176)	0.786	3.673	0.624	-0.224	(-0.475, 0.026)	0.535	1.151	0.078
Total hip aBMD (g/cm^2)	Model 4	0.133	(-0.228, 0.493)	0.489	0.957	0.463	-0.239	(-0.535, 0.058)	0.346	0.529	0.112
Femoral neck aBMD (g/cm^2)	Model 4	0.215	(-0.182, 0.612)	0.381	0.616	0.282	-0.363	(-0.636, -0.091)	0.450	0.818	**0.010**
Lumbar spine aBMD (g/cm^2)	Model 4	0.041	(-0.446, 0.528)	0.076	0.082	0.866	-0.134	(-0.395, 0.127)	0.508	1.033	0.308
Cross-sectional area (cm^2)	Model 4	0.201	(-0.23, 0.632)	0.271	0.372	0.353	-0.228	(-0.459, 0.003)	0.604	1.525	0.053
Cross-sectional moment of inertia (cm^4)	Model 4	0.065	(-0.44, 0.571)	-0.001	-0.001	0.796	-0.012	(-0.199, 0.175)	0.740	2.846	0.899
Section modulus (cm^3)	Model 4	0.110	(-0.372, 0.593)	0.087	0.095	0.647	-0.123	(-0.309, 0.063)	0.743	2.891	0.191
Trabecular bone score	Model 4	0.302	(-0.183, 0.786)	0.088	0.096	0.216	-0.305	(-0.576, -0.034)	0.470	0.887	**0.028**

Multiple linear regression analyses were performed as follows: model 4 (adjusted for sex, time from treatment completion to baseline evaluation [years], radiotherapy exposure [yes/no], region-specific lean mass [g] and calcium intake [mg/day]). Region-specific for total hip, narrow neck cross-sectional area, cross-sectional moment of inertia and section modulus was legs lean mass and for lumbar spine and Trabecular Bone Score was trunk lean mass. Standardized β coefficient, adjusted R^2 and *P* value < .05 are provided in bold. Abbreviations: aBMD, areal bone mineral density (g/cm^2); CI, Confidence interval.

Table S3. Multiple lineal regressions for the associations of watching television less than one hour, N=44 (compared to not watching television, N=21) and bone parameters in prepubertal and peri/post-pubertal young paediatric cancer survivors.

		Pre-pubertal					Peri/post-pubertal				
		B	95% CI	A. R^2	f^2	*P*	B	95% CI	A. R^2	f^2	*P*
Total body less head aBMD (g/cm^2)	Model 1	-0.112	(-0.598, 0.373)	0.036	0.037	.644	-0.285	(-0.593, 0.023)	0.098	0.109	.069
	Model 2	-0.131	(-0.614, 0.351)	0.056	0.059	.587	-0.268	(-0.581, 0.045)	0.100	0.111	.092
	Model 3	-0.008	(-0.241, 0.225)	0.781	3.566	.946	-0.169	(-0.393, 0.056)	0.543	1.188	.138
	Model 4	-0.005	(-0.236, 0.225)	0.786	3.673	.964	-0.172	(-0.399, 0.056)	0.535	1.151	.135
Total hip aBMD (g/cm^2)	Model 1	-0.021	(-0.507, 0.465)	0.032	0.033	.931	-0.225	(-0.538, 0.088)	0.073	0.079	.155
	Model 2	-0.023	(-0.500, 0.455)	0.076	0.082	.924	-0.208	(-0.520, 0.103)	0.111	0.125	.186
	Model 3	0.049	(-0.321, 0.419)	0.448	0.812	.793	-0.108	(-0.378, 0.161)	0.355	0.550	.423
	Model 4	0.055	(-0.301, 0.411)	0.489	0.957	.759	-0.114	(-0.387, 0.158)	0.346	0.529	.403
Femoral neck aBMD (g/cm^2)	Model 1	0.100	(-0.399, 0.600)	-0.021	-0.021	.689	-0.336	(-0.633, -0.038)	0.162	0.193	**.028**
	Model 2	0.077	(-0.411, 0.566)	0.031	0.032	.752	-0.294	(-0.585, -0.002)	0.226	0.292	**.048**
	Model 3	0.146	(-0.246, 0.539)	0.377	0.605	.457	-0.200	(-0.451, 0.052)	0.439	0.783	.117
	Model 4	0.150	(-0.242, 0.542)	0.381	0.616	.445	-0.213	(-0.462, 0.037)	0.450	0.818	.094
Lumbar spine aBMD (g/cm^2)	Model 1	0.016	(-0.492, 0.524)	-0.057	-0.054	.950	-0.333	(-0.630, -0.036)	0.161	0.192	**.029**
	Model 2	0.011	(-0.504, 0.526)	-0.077	-0.071	.965	-0.321	(-0.624, -0.018)	0.156	0.185	**.038**
	Model 3	0.071	(-0.423, 0.565)	0.021	0.021	.774	-0.209	(-0.441, 0.023)	0.517	1.070	.076
	Model 4	0.063	(-0.417, 0.544)	0.076	0.082	.791	-0.212	(-0.447, 0.024)	0.508	1.033	.077
Cross-sectional area (cm^2)	Model 1	0.188	(-0.293, 0.668)	0.056	0.059	.437	-0.261	(-0.567, 0.045)	0.115	0.130	.093
	Model 2	0.180	(-0.306, 0.667)	0.041	0.043	.460	-0.238	(-0.546, 0.070)	0.134	0.155	.127
	Model 3	0.235	(-0.195, 0.665)	0.254	0.340	.276	-0.102	(-0.316, 0.111)	0.596	1.475	.341
	Model 4	0.240	(-0.185, 0.665)	0.271	0.372	.262	-0.113	(-0.325, 0.099)	0.604	1.525	.288
Cross-sectional moment of inertia (cm^4)	Model 1	0.183	(-0.304, 0.670)	0.031	0.032	.454	-0.139	(-0.439, 0.161)	0.146	0.171	.357
	Model 2	0.178	(-0.320, 0.675)	-0.004	-0.004	.476	-0.131	(-0.440, 0.178)	0.126	0.144	.398
	Model 3	0.193	(-0.307, 0.692)	-0.008	-0.008	.443	0.025	(-0.146, 0.195)	0.741	2.861	.774
	Model 4	0.197	(-0.302, 0.695)	-0.001	-0.001	.431	0.019	(-0.153, 0.190)	0.740	2.846	.827
Section modulus (cm^3)	Model 1	0.192	(-0.289, 0.674)	0.051	0.054	.427	-0.204	(-0.508, 0.101)	0.125	0.143	.185
	Model 2	0.181	(-0.310, 0.673)	0.019	0.019	.462	-0.187	(-0.498, 0.124)	0.116	0.131	.233
	Model 3	0.212	(-0.267, 0.692)	0.072	0.078	.378	-0.030	(-0.201, 0.141)	0.741	2.861	.725
	Model 4	0.217	(-0.259, 0.693)	0.087	0.095	.363	-0.038	(-0.208, 0.133)	0.743	2.891	.660
Trabecular bone score	Model 1	0.219	(-0.277, 0.716)	-0.010	-0.010	.380	-0.320	(-0.599, -0.04)	0.257	0.346	**.026**
	Model 2	0.200	(-0.268, 0.668)	0.110	0.124	.395	-0.330	(-0.617, -0.044)	0.246	0.326	**.025**
	Model 3	0.184	(-0.290, 0.657)	0.100	0.111	.439	-0.244	(-0.490, 0.002)	0.456	0.838	.052
	Model 4	0.182	(-0.295, 0.658)	0.088	0.096	.448	-0.258	(-0.502, -0.014)	0.470	0.887	**.039**

Multiple linear regression analyses with several models of adjustment were performed as follows: model 1 (adjusted for sex), model 2 (adjusted for sex, time from treatment completion to baseline evaluation [years] and radiotherapy exposure [yes/no]), model 3 (adjusted for sex, time from treatment completion to baseline evaluation [years], radiotherapy exposure [yes/no] and region-specific lean mass [g]) and model 4 (adjusted for sex, time from treatment completion to baseline evaluation [years], radiotherapy exposure [yes/no], region-specific lean mass [g] and calcium intake [mg/day]). Region-specific for total hip, narrow neck cross-sectional area, cross-sectional moment of inertia and section modulus was legs lean mass and for lumbar spine and Trabecular Bone Score was trunk lean mass. Standardized β coefficient, adjusted R^2 and *P* value < .05 are provided in bold. Abbreviations: aBMD, areal bone mineral density (g/cm^2); CI, Confidence interval; TV, television.

Chapter 7. Every move counts to improve bone health at clinical sites in young pediatric cancer survivors: the iBoneFIT project

Abstract

Purpose. We aimed to examine the associations of 24-hour movement behaviors (MVPA, light physical activity [LPA], SB and sleep) with age-, sex- and race-specific aBMD Z-score parameters at clinical sites in young pediatric cancer survivors.

Methods. This cross-sectional multicenter study was carried out within the iBoneFIT framework in which 116 young pediatric cancer survivors (12.1±3.3 years old; 42% female) were recruited. We obtained anthropometric and body composition data (i.e., body mass, stature, body mass index and region-specific lean mass), time spent in movement behaviors over at least seven consecutive 24-hour periods (wGT3x-BT accelerometer, ActiGraph) and aBMD Z-score parameters (age-, sex- and race-specific total at the body, total hip, femoral neck and lumbar spine). Survivors were classified according to somatic maturity (pre or peri/post-pubertal depending on the estimated years from PHV). The adjusted models' coefficients were used to predict the effect of reallocating time proportionally across behaviors on the outcomes.

Results. In pre-pubertal young pediatric cancer survivors, reallocating time to MVPA from LPA, SB and sleep was significantly associated with higher aBMD at total body (B=1.765, P=.005), total hip (B=1.709, P=.003) and lumbar spine (B=2.093, P=.001). In peri/post-pubertal survivors, reallocating time to LPA from MVPA, SB and sleep was significantly associated with higher aBMD at all sites (B=2.090 to 2.609, P=.003 to .038). Reallocating time to SB from MVPA or LPA was significantly associated with lower aBMD at most sites in pre-pubertal and peri/post-pubertal survivors, respectively. Finally, reallocating time to sleep from MVPA, LPA and SB was significantly associated with lower aBMD at total body (B=-2.572, P=.036) and total hip (B=-3.371, P=.015).

Conclusions. These findings suggest that every move counts and underline the benefits of increasing MVPA or LPA, when low MVPA levels are present, for bone regeneration following pediatric cancer treatment completion.

Introduction

Pediatric cancer survival has experienced a remarkable increase during the last decades, with a 5-year survivorship rate of 85% in children and 82% in adolescents [1]. However, low aBMD, defined by age-, sex- and race-specific aBMD Z-score less than -1, has been shown in up to two-thirds of survivors [2]. Childhood is a crucial period for skeletal maturity and growth [3], and pediatric cancer occurs during this critical period for bone mass acquisition [4]. In this regard, bone development differs depending on chronological age and/or somatic maturation, but the latter is more appropriate during childhood and adolescence [5]. Moreover, a lifestyle factor such as physical activity may contribute to bone development [6].

The international physical activity guidelines for pediatric cancer survivors underline the importance of engaging in at least an average of 60 min of MVPA per day and limiting SB [7,8]. However, only one-third of survivors meet these recommendations even years after pediatric cancer diagnosis (7.0 $\pm$ 3.3 years) [9]. Self-reported physical activity has been associated with higher total body aBMD [10], and lumbar spine aBMD Z-score [10-12] in survivors. Additionally, previous studies using both objective and self-reported methods did not show robust associations of SB with lower total body and lumbar spine aBMD Z-score [12-14]. Research in children and adolescents does not consistently show associations of sleep with aBMD parameters [15] while short sleep has been reported in almost half of 911 adult pediatric cancer survivors [16]. The existing literature regarding the associations of physical activity, SB and sleep with bone health in young pediatric cancer survivors is limited by important knowledge gaps including self-reported measures, small sample sizes and methodological shortcomings. Therefore, investigating the associations of 24-hour movement behaviors (MVPA, LPA, SB, and sleep) with bone health is important for the identification of behavioral patterns capable of inducing benefits on bone health in young pediatric cancer survivors.

The 24-hour continuum, which considers movement behaviors as dependent of each other, has raised more attention in the recent years [17]. In comparison to isotemporal substitution models which have commonly been used to investigate time reallocation across behaviors [18] and linear regression models, compositional data analysis is not affected by multicollinearity. Moreover, previous studies investigating movement behaviors and bone health have not accounted for the co-dependency of movement behaviors which may produce spurious findings as it is impossible to increase the daily time in one behavior while maintaining the rest constant [19,20].

The aim of this study was to examine the associations of 24-hour movement behaviors (MVPA, LPA, SB, and sleep) with age-, sex- and race-specific aBMD parameters at clinical sites in pre-pubertal and peri/post-pubertal cancer survivors using compositional data analysis.

Methods

Study design and population

This cross-sectional study refers to baseline data from the iBoneFIT project and includes 116 young pediatric cancer survivors (12.1±3.3 years; 42% female). A detailed description of the study protocol has been published together with the sample size calculation elsewhere [21]. Briefly, iBoneFIT is a multicenter parallel group RCT designed to examine the effect of a 9-month online exercise program on bone health in young pediatric cancer survivors [21]. Survivors were recruited from the Units of Pediatric Oncology and Hematology of the 'Virgen de las Nieves' (Granada) and 'Reina Sofia' (Cordoba) University Hospitals. Inclusion criteria were being aged from 6 to 18 years, not currently receiving treatments for cancer, diagnosed one year earlier at minimum and having been exposed to radiotherapy and/or chemotherapy. All measurements were conducted during Autumn and Winter and in two waves due to COVID- 19 restrictions: first, from October to February 2020/2021; and the second from December to March 2021/2022. In short and for the purpose of this study, we included demographics data (i.e., sex, age), body composition data (i.e., body mass, stature, body mass index and region-specific lean mass), clinical data (time from treatment completion [years] and radiotherapy exposure [yes/no]), time spent in movement behaviors over at least seven consecutive 24-hour periods (wGT3x-BT accelerometer, ActiGraph) and aBMD parameters (age-, sex- and race-specific total body, total hip, femoral neck and lumbar spine). All survivors provided written informed consent and/or assent before entering the trial. When they were younger than 12 years old, parents provided them. The iBoneFIT project was approved by the Ethics Committee on Human Research of Regional Government of Andalusia (Reference: 4500, December 2019), followed the ethical guidelines of the Declaration of Helsinki (revised version 2013) and the RCT was registered (https://www.isrctn.com/ISRCTN61195625). This study is reported according to the STROBE checklist (**Table S1**). Although we recruited a total of 116 survivors, sample size may slightly vary for some variables due to missing data (i.e., some survivors were afraid of being scanned using DXA or even not willing to collaborate on testing day).

Anthropometry and somatic maturity

Body mass (kg) was evaluated with an electronic scale (SECA 861, Hamburg, Germany) with an accuracy of 100 g. Stature (cm) was assessed using a precision stadiometer (SECA 225, Hamburg, Germany) to the nearest 0.1 cm. Body mass index was calculated as body mass (kg)/height (m^2). Somatic maturity was measured using the prediction of estimated years before or after PHV using validated algorithms for boys and girls [22].

Clinical data

Given that long-lasting oncological treatment has more dreaded effects on bone health [23] and aBMD may improve with increasing time-off therapy [24], time from treatment completion to baseline evaluation was calculated. Likewise, due to some treatments such as radiotherapy are strong risk factors for low aBMD in young pediatric cancer survivors [25], information on the type of treatment of treatment (radiotherapy, chemotherapy and/or surgery, alone or in combination) was obtained from the survivors' medical records. Then, a dichotomic variable based on the treatment type (radiotherapy; yes/no) was computed and used as a covariate.

Movement behaviors

MVPA, LPA, SB and sleep were measured using the wrist-worn tri-axial ActiGraph wGT3x-BT accelerometer (ActiGraph GT3X, Pensacola, FL, USA) for seven consecutive days (24 hours/day). Young pediatric cancer survivors were instructed to wear devices always attached to the non-dominant wrist except for water activities. To assist the sleep-detection algorithm, survivors were instructed to report the time they got in bed and out of bed every day. Accelerometers were initialized at a sampling frequency of 90 Hz and raw data were processed using the GGIR R open-source package. Euclidean Norm of the raw acceleration minus one G with negative values rounded to zero (ENMO) was calculated, as well as the angle of the z-axis of the device to estimate physical activity and sleep parameters [26]. Non-wear time was detected based on the standard deviation of the raw accelerations recorded in the three accelerometer axes as described elsewhere [27], and then imputed by means of the acceleration in the rest of the days at the same time window. Appropriate thresholds were used to identify physical activity intensities and SB (i.e., MVPA: 200 mg, LPA: 35-200 mg, SB: 35 mg) [28]. We considered a day valid when the accelerometer registered at least 23 hours and the survivors wore it at least for 16 hours. Survivors having at least one valid day (only one survivor) were included (sensibility analyses showed similar results when compared to survivors having at least three valid weekdays and one weekend day). Daily average MVPA, LPA, SB and sleep were calculated as the mean of all seven days.

Dual-energy X-ray absorptiometry (DXA)

All young pediatric cancer survivors were evaluated using a single DXA scanner (Hologic Series Discovery QDR, Bedford, MA, USA) and analyzed by APEX software (version 4.0.2). The device was calibrated each day using a lumbar spine phantom. Survivors were asked to remain still and scanned in the supine position. The positioning of the survivors and the analyses of the results were undertaken according to the International Society of Clinical Densitometry [29]. Three scans (total body, right hip and lumbar spine) were performed to obtain aBMD (g/cm^2) of the total body (less head), total hip, femoral neck and lumbar spine (mean of L1–L4). The three scans were also used to obtain lean mass (g) [body mass – (fat mass + bone mass)] of the total body, legs and trunk. DXA coefficient of variation in pediatric population ranges between 1.0 and 2.9%, depending on the region [30].

Data Analyses

The normal distribution of the variables was checked and verified using Kolmogorov-Smirnov test, skewness and kurtosis values, visual check of histograms, Q-Q and box plots. Descriptive data were reported as mean and SD or as frequencies (percentages). Interaction analyses were performed between movement behaviors variables and sex on the outcomes. No significant interactions were found (P>.05), so analyses were carried out for boys and girls together.

Using international reference data of healthy children and adolescents from the Bone Mineral Density in Childhood Study [31], age-, sex- and race-specific aBMD Z-score at total body, total hip, femoral neck and lumbar spine were calculated for the main analysis. Compositional data analysis was used to investigate the associations of movement behaviors (MVPA, LPA, SB, and sleep) with aBMD Z-score parameters. This type of analysis investigates the reallocation of time across behaviors over a specified continuum (i.e., 24-hour) while lowering the risk of multicollinearity [17,32]. First, we calculated isometric log-ratios in sequential binary partition as previously proposed [17] and were included as explanatory variables. The non-standardized B coefficient represents the strength and direction of the association of each behavior relative to the rest of behaviors in the composition with an outcome (i.e., total body aBMD). The models' coefficients were then used to predict the effect of reallocating time proportionally across behaviors (i.e., increasing MVPA while reducing the remaining behaviors) and pairwise (i.e., increasing MVPA while reducing SB) on the outcomes. The results can be interpreted as the hypothetical change in the outcome associated with reallocating time between behaviors for a hypothetical average pre-pubertal or peri/post-

pubertal cancer survivor in our sample as the model coefficients are relative to the mean time-use composition. We fitted an adjusted model with the isometric log-ratios between the behaviors, time from treatment completion, radiotherapy exposure and region-specific lean mass. The latter was used for regional aBMD parameters instead of total lean mass because of the specific adaptations of the skeleton region [33]. Therefore, the chosen region-specific adjustment for total hip and femoral neck was legs lean mass while for lumbar spine was trunk lean mass. The covariates selection was based on their relationship with aBMD parameters [34-36]. Moreover, given the relevance of somatic maturity in the bone development process, survivors were split in two groups according to their maturity offset, as previously reported: pre-pubertal (<-1 year from PHV) and peri/post-pubertal (>-1 year from PHV) [37]. Statistical analyses were performed using the statistical software R version 4.0.3 (R Foundation for Statistical Computing) and two-sided P-values <.05 were considered statistically significant.

Results

Participants

Descriptive characteristics of our sample are presented by somatic maturity groups (**Table 1**) and by sex in **Table S2**. The distribution of cancer types is shown for the whole sample and by somatic maturity groups (**Table S3**). The distribution of MVPA, LPA and SB is displayed in ternary plots by somatic maturity groups in **Figure 1**. The geometric means showed that pre-pubertal survivors tended to be more physically active and less sedentary than peri/post-pubertal survivors (**Table 2**). The covariance matrices for the daily time-use in movement behaviors by somatic maturity groups are presented in **Table 3**.

Predicted associations of MVPA and LPA with aBMD parameters

In pre-pubertal cancer survivors, the dose-response curves and the effect sizes relative to increase MVPA, while proportionally reducing LPA, SB and sleep were positively significant on aBMD at total body (B=1.765, P=.005), total hip (B=1.709, P=.003) and lumbar spine (B=2.093, P=.001; **Figure 2**). The dose-response curves of the pairwise reallocation plots illustrated a significant positive effect of replacing LPA, SB or sleep with MVPA on aBMD at total body, total hip and lumbar spine in pre-pubertal survivors (**Figure 2**). In peri/post-pubertal cancer survivors, the dose-response curves and the effect sizes relative to increase LPA, while proportionally reducing MVPA, SB and sleep were positively significant on aBMD at total body (B=2.609, P=.003), total hip (B=2.591, P=.008), femoral neck (B=2.479, P=.012) and lumbar spine (B=2.090, P=.038; **Figure 3**). The dose-response curves of the pairwise

reallocation plots did not illustrate a significant effect of replacing MVPA with LPA on aBMD parameters in peri/post-pubertal survivors (**Figure 3**). However, in pre-pubertal survivors, replacing MVPA with LPA showed a significant negative effect on aBMD at total body, total hip and lumbar spine. Conversely, replacing SB or sleep with LPA illustrated a significant positive effect on aBMD at total body and femoral neck, and at all sites in peri/post-pubertal survivors, respectively.

Predicted associations of SB and sleep with aBMD parameters

The dose-response curves and the effect sizes relative to increase SB, while proportionally reducing MVPA, LPA and sleep were not significant on any aBMD parameters neither in pre-pubertal nor in peri/post-pubertal cancer survivors (**Figure 4**). In pre-pubertal survivors, the dose-response curves of the pairwise reallocation plots illustrated a significant negative effect of replacing MVPA with SB on aBMD at total body, total hip and lumbar spine (**Figure 4**). In peri/post-pubertal survivors, replacing LPA with SB illustrated a significant negative effect on aBMD at total body, total hip and femoral neck, while replacing sleep with SB presented a significant positive effect on aBMD at total hip. In peri/post-pubertal cancer survivors, the dose-response curves and the effect sizes relative to increase sleep, while proportionally reducing MVPA, LPA and SB were negatively significant on aBMD total body (B=-2.572, P=.036) and total hip (B=-3.371, P=.015; **Figure 5**). In pre-pubertal survivors, the dose-response curves of the pairwise reallocation plots illustrated a significant negative effect of replacing MVPA with sleep on aBMD at total body, total hip and lumbar spine only in pre-pubertal survivors (**Figure 5**). In peri/post-pubertal survivors, replacing LPA with sleep illustrated a significant negative effect on aBMD at all sites, whereas replacing SB with sleep did not illustrate any significant effect on aBMD parameters.

Table 1. Descriptive characteristics of the survivors included in the study.

	Total	N	Prepubertal	N	Peri/post-pubertal	N
Sex (female/male, %)	42.2/57.8	116	37.9/62.1	58	46.5/53.5	58
Age (years)	12.1 (3.3)	116	9.3 (1.8)	58	14.9 (1.7)	58
Body mass (kg)	46.6 (18.0)	116	34.1 (9.3)	58	59.1 (16)	58
Stature (cm)	147.5 (17.1)	116	133.4 (10.9)	58	161.6 (8)	58
Body mass index (kg/m^2)	20.7 (4.7)	116	18.9 (3.3)	58	22.5 (5.2)	58
Estimated years from peak height velocity	-0.8 (2.7)	116	-3.1 (1.2)	58	1.6 (1.5)	58
Time from treatment completion (years)	5.0 (3.8)	113	3.4 (2.6)	56	6.6 (4.1)	57
Radiotherapy exposure (yes/no, %)	27.6/72.4	116	25.9/74.1	58	29.3/70.7	58
Lean mass (kg)						
Total body less head	25.7 (10.4)	116	18.0 (5.0)	58	33.5 (8.4)	58
Legs	4.6 (2.0)	116	3.2 (1.0)	58	6.0 (1.6)	58
Trunk	14.3 (5.6)	116	10.1 (2.6)	58	18.6 (4.4)	58
aBMD Z-score						
Total body less head	-0.2 (1.4)	116	-0.1 (1.4)	58	-0.3 (1.3)	58
Total hip	0.1 (1.3)	115	0.3 (1.2)	58	0.0 (1.4)	57
Femoral neck	-0.2 (1.4)	115	-0.2 (1.4)	58	-0.2 (1.4)	57
Lumbar spine	-0.1 (1.3)	116	0.0 (1.3)	58	-0.1 (1.4)	58

Data are presented as mean (standard deviation) or as frequencies (percentages), as indicated. Areal bone mineral density (aBMD) Z-score parameters are presented using international reference data from the Bone Mineral Density in Childhood. Abbreviations: aBMD, areal bone mineral density.

Table 2. Geometric mean for the daily time-use in movement behaviors.

	Pre-pubertal (min/day)	Peri/post-pubertal (min/day)
MVPA	52.7	21.2
LPA	283.4	223.3
SB	556.0	697.5
Sleep	547.9	498.0

Abbreviations: MVPA, moderate-to-vigorous physical activity; LPA, light physical and SB, sedentary behavior.

Table 3. Covariance matrices for the daily time-use in movement behaviors.

	MVPA	LPA	SB	Sleep
Pre-pubertal				
MVPA		0.13	0.32	0.22
LPA	0.13		0.12	0.06
SB	0.32	0.12		0.03
Sleep	0.22	0.06	0.03	
	MVPA	LPA	SB	Sleep
Peri/post-pubertal				
MVPA		0.36	0.65	0.56
LPA	0.36		0.12	0.08
SB	0.65	0.12		0.03
Sleep	0.56	0.08	0.03	

Note: values close to 0 represent high covariance (dependence) between the variables.
Abbreviations: SB, sedentary behavior; LPA, light physical activity; MVPA, moderate-to-vigorous physical activity.

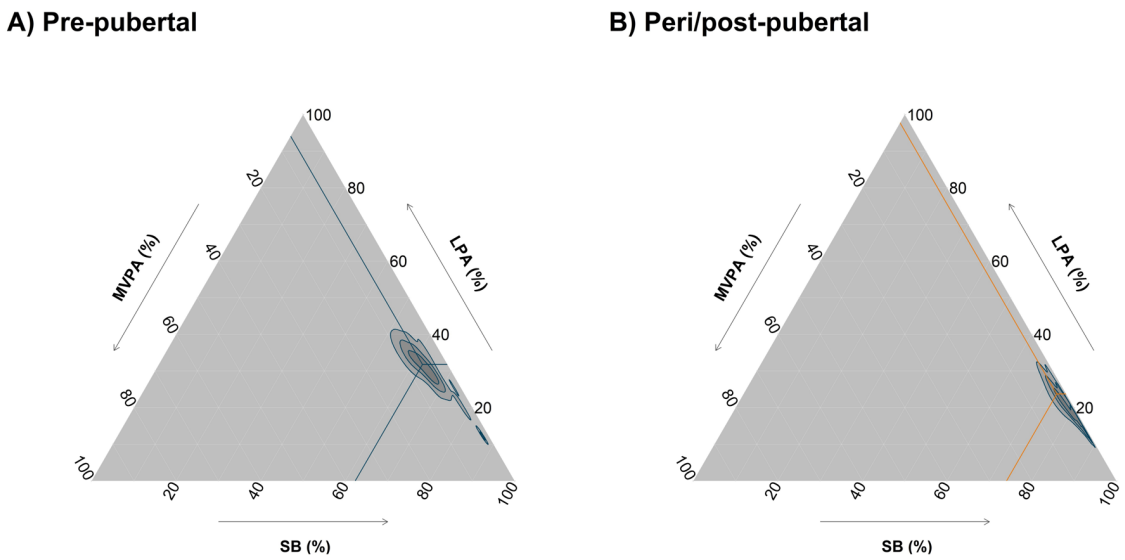

Figure 1. Radar plots visualisation of the multiple regression model for areal bone mineral density parameters (total body less head, femoral neck, lumbar spine, total hip, legs and arms) and the standardised β coefficient of each predictor. Abbreviations: aBMD, areal bone mineral density; PA, physical activity.

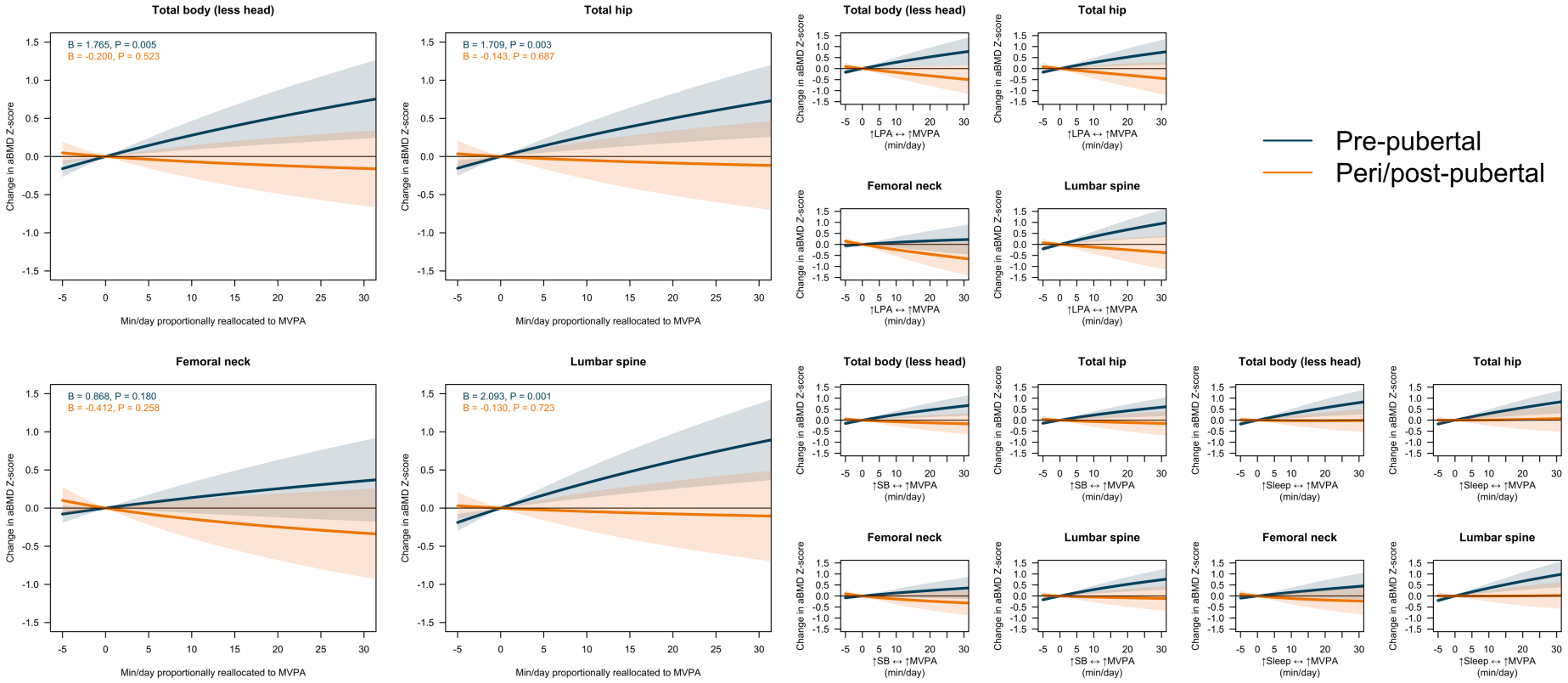

Figure 2. Predicted associations of moderate-to-vigorous physical activity (MVPA) relative to light physical activity (LPA), sedentary behavior (SB), and sleep with age-, sex- and race-specific areal bone mineral density (aBMD) Z-score parameters in pre-pubertal and peri/post-pubertal cancer survivors. The lines represent the expected change in the aBMD Z-score parameters upon increasing the dominant behavior, while proportionally reducing the others. Age-, sex- and race-specific aBMD Z-score parameters at clinical sites are presented using international reference data from the Bone Mineral Density in Childhood Study [31]. All models adjusted by rest of movement behaviors, time from treatment completion, radiotherapy exposure and region-specific lean mass. The chosen region-specific adjustment for total hip and femoral neck was legs lean mass and for lumbar spine was trunk lean mass.

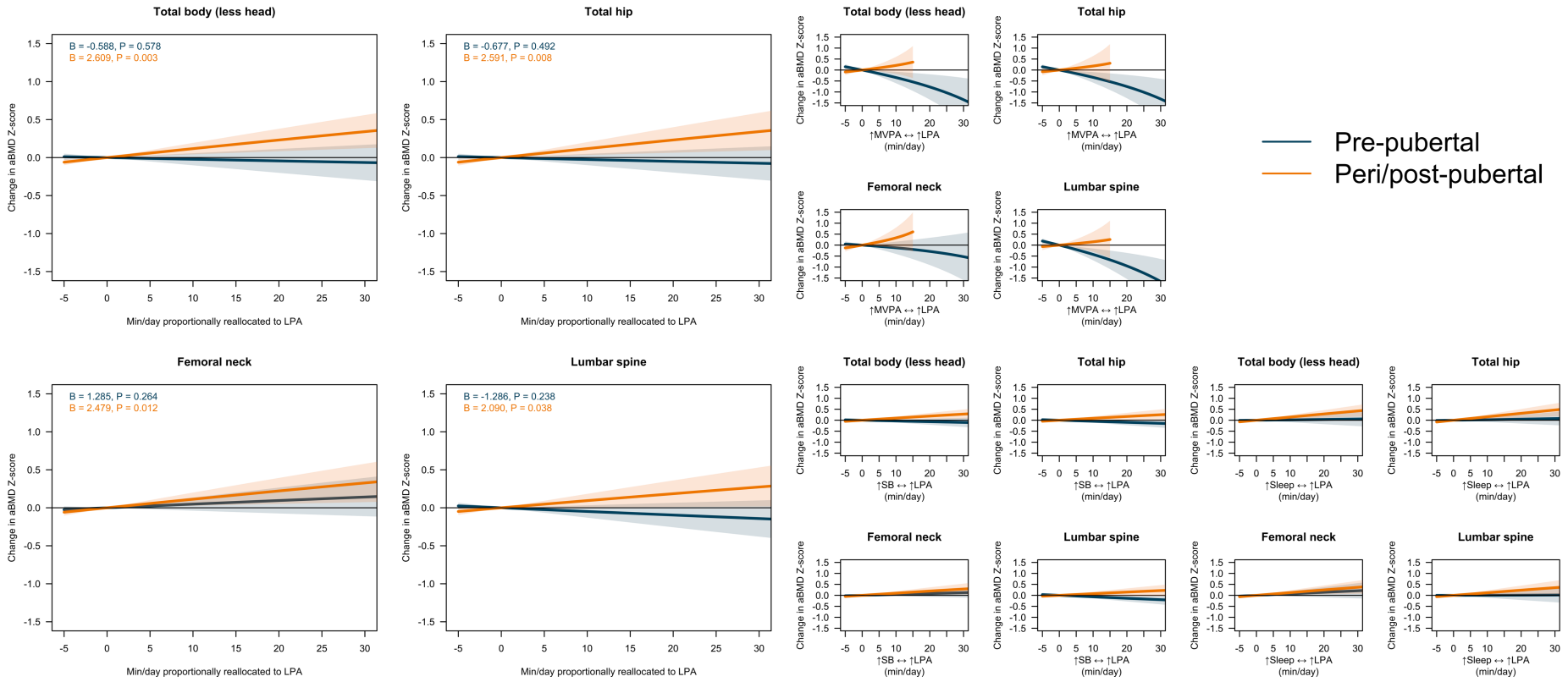

Figure 3. Predicted associations of light physical activity (LPA) relative to moderate-to-vigorous physical activity (MVPA), sedentary behavior (SB) and sleep with age-, sex- and race-specific areal bone mineral density (aBMD) Z-score parameters in pre-pubertal and peri/post-pubertal cancer survivors. The lines represent the expected change in the aBMD Z-score parameters upon increasing the dominant behavior, while proportionally reducing the others. Age-, sex- and race-specific aBMD Z-score parameters at clinical sites are presented using international reference data from the Bone Mineral Density in Childhood Study [31]. All models adjusted by rest of movement behaviors, time from treatment completion, radiotherapy exposure and region-specific lean mass. The chosen region-specific adjustment for total hip and femoral neck was legs lean mass and for lumbar spine was trunk lean mass.

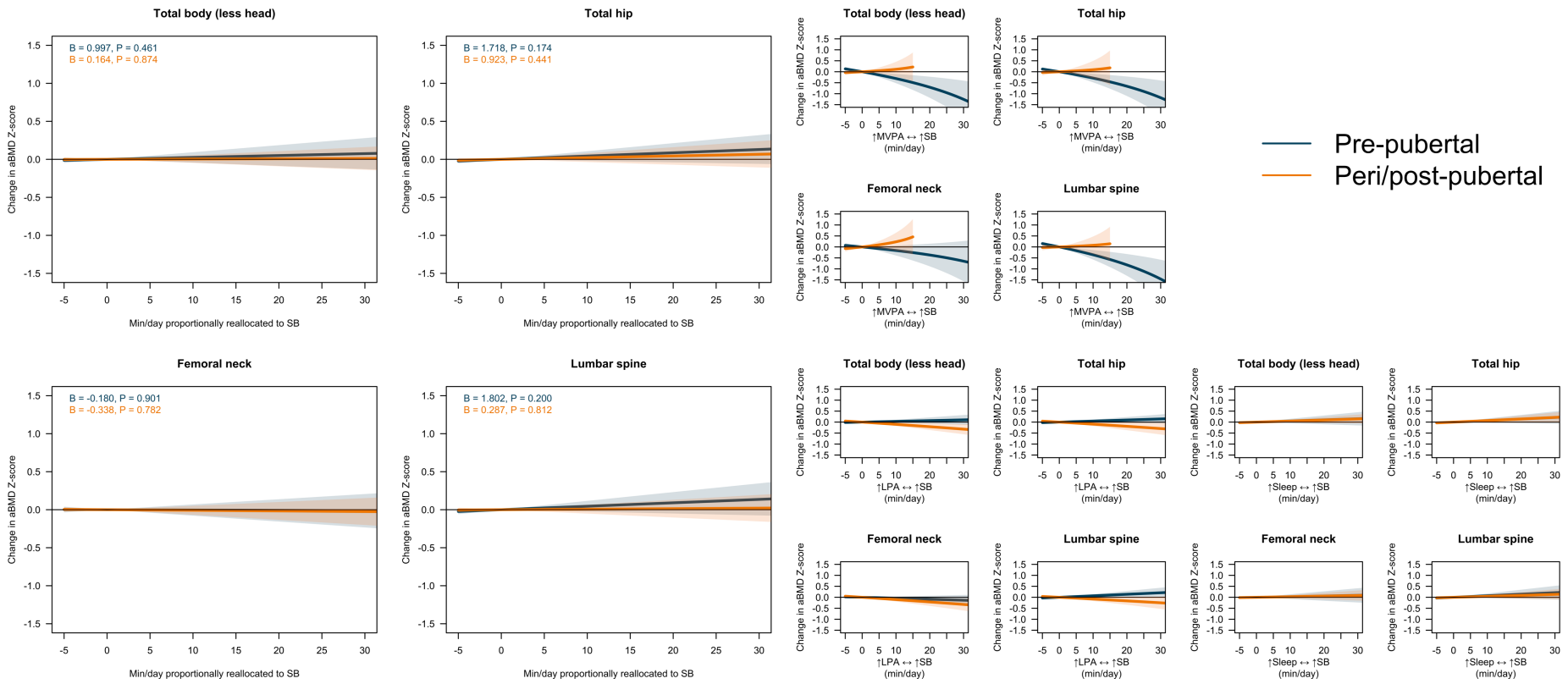

Figure 4. Predicted associations of sedentary behavior (SB) relative to moderate-to-vigorous physical activity (MVPA), light physical activity (LPA) and sleep with age-, sex- and race-specific (aBMD) Z-score parameters in pre-pubertal and peri/post-pubertal cancer survivors. The lines represent the expected change in the aBMD Z-score parameters upon increasing the dominant behavior, while proportionally reducing the others. Age-, sex- and race-specific aBMD Z-score parameters at clinical sites are presented using international reference data from the Bone Mineral Density in Childhood Study [31]. All models adjusted by rest of movement behaviors, time from treatment completion, radiotherapy exposure and region-specific lean mass. The chosen region-specific adjustment for total hip and femoral neck was legs lean mass and for lumbar spine was trunk lean mass.

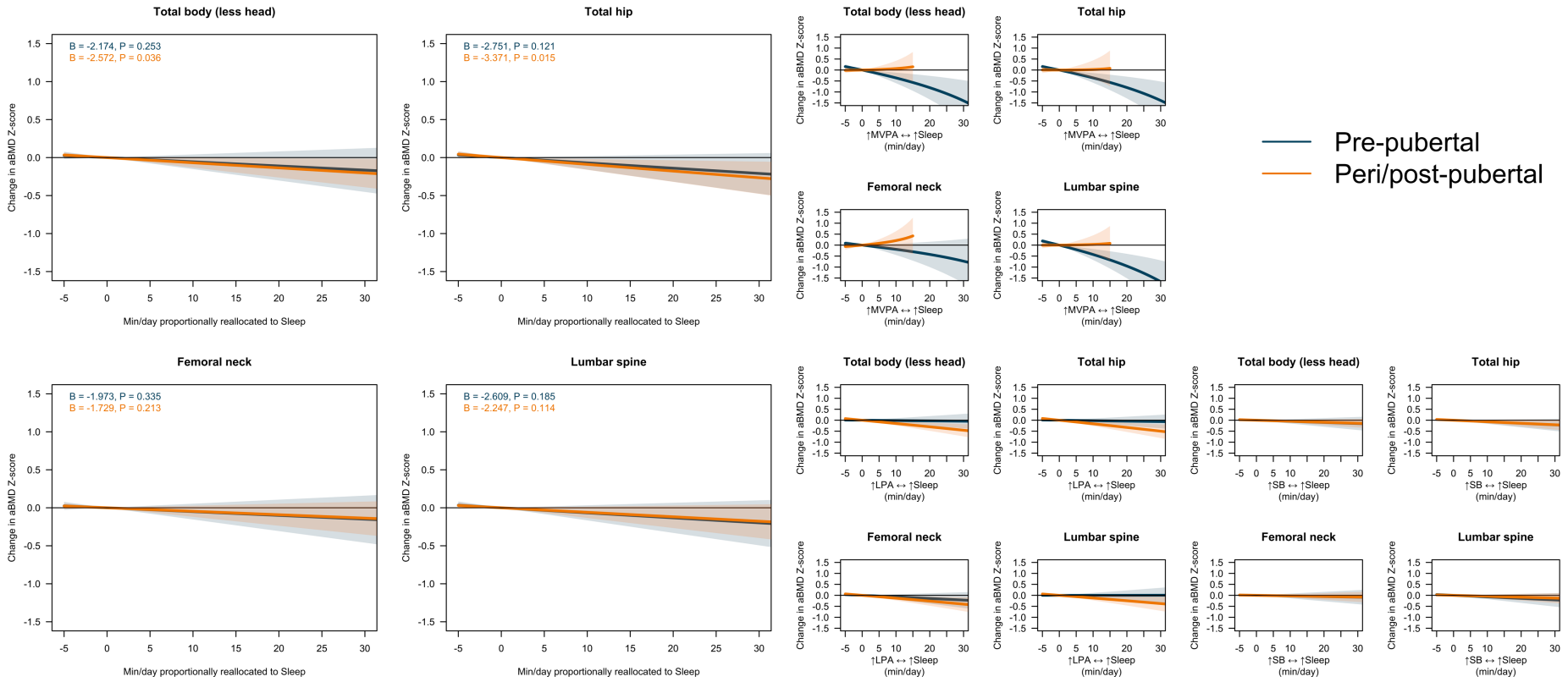

Figure 5. Predicted associations of sleep relative to moderate-to-vigorous physical activity (MVPA), light physical activity (LPA) and sedentary behavior (SB) with age-, sex- and race-specific (aBMD) Z-score parameters in pre-pubertal and peri/post-pubertal cancer survivors. The lines represent the expected change in the aBMD Z-score parameters upon increasing the dominant behavior, while proportionally reducing the others. Age-, sex- and race-specific aBMD Z-score parameters at clinical sites are presented using international reference data from the Bone Mineral Density in Childhood Study [31]. All models adjusted by rest of movement behaviors, time from treatment completion, radiotherapy exposure and region-specific lean mass. The chosen region-specific adjustment for total hip and femoral neck was legs lean mass and for lumbar spine was trunk lean mass.

Discussion

In this novel study, the predicted associations of MVPA with higher aBMD were significant at most sites in pre-pubertal young pediatric cancer survivors. In peri/post-pubertal survivors with low MVPA levels (21.2 min/day), LPA was significantly associated with higher aBMD at all sites. Additionally, replacing MVPA or LPA with SB was significantly associated with lower aBMD at most sites in pre-pubertal and peri/post-pubertal survivors, respectively. These results are consistent with the hypothesis that every move counts to maximize bone development after pediatric cancer treatment completion. These findings provide objective results on the key role of movement behaviors for bone health and further reinforce the international physical activity guidelines for pediatric cancer survivors [7,8].

Predicted associations of MVPA and LPA with aBMD parameters

To the best of our knowledge, no study has investigated the associations of objectively measured 24-hour movement behaviors (MVPA, LPA, SB, and sleep) with aBMD Z-scores at clinical sites in young pediatric cancer survivors. In healthy children aged two to five years, Taylor et al. [38] found that increasing MVPA, while proportionally reducing LPA, SB and sleep was significantly associated with higher total body aBMD using compositional data analysis, partially similar to our findings. Likewise, using self-reported methods, one study showed significant correlations between physical activity levels and higher total body aBMD Z-score in pediatric cancer survivors [10], which is partially in line with our results. However, authors did not account for somatic maturity differences, even though survivors' age range was remarkably wide (4-32 years). On the contrary, Kadan-Lottick et al. [39] and Polgreen et al. [12] did not find similar findings. Some of the reasons that might explain why our results differ are that somatic maturity differences (49% survivors were pre-pubertal) were not considered by Kadan-Lottick et al. [39] and the different physical activity levels and/or intensities were not accounted by Polgreen et al. [12].

Concerning total hip and femoral neck aBMD, Bordbar et al. [40] showed that physical activity levels were not significantly associated with femoral neck aBMD Z-score in acute lymphoblastic leukemia survivors (mostly pre-pubertal), which agrees with our findings. Similarly, in young adult pediatric cancer survivors, two studies [41,42] did not find significant associations of physical activity levels with total hip nor femoral neck aBMD Z-score, which is in partial agreement with our findings since these survivors' somatic maturity was greater than that of our peri/post pubertal group.

Regarding lumbar spine aBMD, previous reports have shown that physical activity levels were significantly associated with higher lumbar spine aBMD Z-score [10-12]. However, these findings do not fully agree with ours since the included survivors in these studies were mostly peri/post-pubertal. Altogether, the reason why we did not find MVPA to be significantly associated with higher aBMD in our peri/post-pubertal survivors might be due to their low levels (21.2 min/day). For this reason, when the time spent in MVPA is around the recommended levels such as in our pre-pubertal survivors, most reallocations showed significant positive effects on aBMD parameters, which is in line with previous records [43,44]. However, given the lack of robust control in previous studies, it cannot be further confirmed whether our different results between pre-pubertal and peri/post-pubertal survivors are due to somatic maturity differences. In healthy children and adolescents with different somatic maturity groups, physical activity interventions have provided evidence of the remarkable responsiveness of bone cells during the pre-pubertal stage [45,46]. Therefore, more studies are needed to confirm our findings in survivors.

All previous-mentioned studies in young pediatric cancer survivors did not distinguish physical activity intensities and hence, this hampers further comparisons with our findings increasing LPA. Previous reports in healthy children and adolescents have demonstrated the high impact of MVPA on aBMD parameters [43,44]. However, when low MVPA levels were present, increasing LPA while proportionally reducing MVPA, SB and sleep has been significantly associated with higher total body aBMD using compositional data analysis [38]. Moreover, LPA has been shown to decelerate age-related bone loss in older adults [47]. These positive findings of LPA align with our results in peri/post-pubertal survivors who also had low MVPA levels (21.2 min/day). For this reason, when low MVPA levels are not present, replacing MVPA with LPA did not illustrate a significant positive effect on aBMD at any sites in pre-pubertal survivors. Moreover, the replacement of SB or sleep with LPA in peri/post-pubertal survivors showed a significant positive effect on aBMD at most sites. These findings illustrated that every move count to enhance bone regeneration after pediatric cancer treatment completion. Nevertheless, the some of the above-mentioned results might be limited by self-reported methods to accurately measure the different physical activity levels and/or intensities. Adding objective methods such as accelerometers and analyses accounting for the co-dependency of 24-hour movement in young pediatric survivors would provide more valid and reliable findings.

Predicted associations of SB and sleep with aBMD parameters

Reallocating time to SB from MVPA, LPA and sleep was not significantly associated with total body aBMD in healthy children aged from two to five years using compositional data analysis [38]. Using self-reported methods, two studies [12,13] including pre-pubertal and peri/post-pubertal survivors together reported that screen time were significantly associated with lower total body and lumbar spine aBMD Z-score which partially agrees with our findings. Conversely, Kelly et al. [14] reported that screen time was not significantly associated with total body aBMD Z-score, but the age range of the included survivors was quite wide (3-19 years) and authors did not account for somatic maturity differences. Therefore, analyses divided by somatic maturity groups could have shown different results. Our findings showed the significant negative effect of SB on aBMD at most sites when replacing MVPA or LPA with SB in pre-pubertal and peri/post-pubertal survivors, respectively. This also illustrated the important role of MVPA and LPA (when low MVPA levels) for bone health.

Increasing sleep, while proportionally reducing MVPA, LPA and SB was negatively associated with total body aBMD in healthy children aged five years old using compositional data analysis [38]. Likewise, we found significant associations with reduced aBMD at total body and total hip when increasing sleep. In healthy children and adolescent, there seems to be an optimal duration of sleep, beyond which its beneficial associations with aBMD parameters may decline [48]. This might explain our findings because excessive sleep leaves less time available for MVPA and LPA and therefore, the absence of mechanical strains elicited by physical activity could possibly affect bone development [49]. Therefore, increasing sleep time does not seem to be an effective strategy to improve aBMD parameters. Nevertheless, future studies are needed to confirm these results with objective methods (i.e., accelerometers) since self-reported methods to measure SB and sleep might be particularly less appropriate in young population which could also explain these contrary results [50].

Limitations

Our findings should be interpreted with caution as certain limitations exist. First, albeit we controlled for relevant covariates, residual confounding cannot be eliminated. Second, the cross-sectional design does not enable to examine the causality of the findings and our time reallocation analyses are based on the observed time-use compositions across young pediatric cancer survivors and not on actual within-survivors changes in the time-use composition. Therefore, longitudinal studies are needed to confirm our positive findings. Additionally, the calculation of the estimated years from the PHV is not recommended for children under the age of eight years [22]. Nevertheless, we included 16 survivors younger than eight years old to

calculate this estimate because it did not affect our classification in different somatic maturity groups and so, the main findings.

Clinical and public health relevance

Previously, the focus for young pediatric survivors has commonly been on meeting the physical activity international guidelines for healthy children and adolescents [51]. However, although it may well be challenging to engage in at least an average of 60 min of MVPA and limit SB through cancer continuum, our findings showed that reallocating time to MVPA or LPA from SB was significantly associated with higher aBMD at most sites in pre-pubertal and peri/post-pubertal survivors, respectively. This underlines the public health implications of these findings after pediatric cancer treatment completion.

Conclusions

In this observational study, the predicted associations of MVPA with higher aBMD were significant at most sites in pre-pubertal young pediatric cancer survivors. In peri/post-pubertal survivors with low MVPA levels, LPA was significantly associated with higher aBMD at all sites. Moreover, replacing MVPA or LPA with SB was significantly associated with lower aBMD at most sites in pre-pubertal and peri/post-pubertal survivors, respectively. These findings suggest that every move counts and underline the benefits of increasing MVPA or LPA to maximize bone regeneration following pediatric cancer treatment completion.

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Supplementary material

Table S1. STROBE Statement-Checklist of items that should be included in reports of *cross-sectional studies.*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	149
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	149
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	150-151
Objectives	3	State specific objectives, including any prespecified hypotheses	150-151
Methods			
Study design	4	Present key elements of study design early in the paper	151
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	151
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	151
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	151-153
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	151-153
Bias	9	Describe any efforts to address potential sources of bias	153-154
Study size	10	Explain how the study size was arrived at	151
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	151-153
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	153-154
		(*b*) Describe any methods used to examine subgroups and interactions	153-154
		(*c*) Explain how missing data were addressed	153-154

		(*d*) If applicable, describe analytical methods taking account of sampling strategy	153-154
		(*e*) Describe any sensitivity analyses	153-154
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Not applicable
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, Tables S2-4 and Figure 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1, Tables S2-4 and Figure 1
Outcome data	15	Report numbers of outcome events or summary measures	Table 1 and Tables S2-4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figure 2, 3, 4 and 5
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	154-155
Discussion			
Key results	18	Summarise key results with reference to study objectives	163
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	165-166
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	163-166
Generalisability	21	Discuss the generalisability (external validity) of the study results	166

Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

Note: An explanation and elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Table S2. Descriptive characteristics of the survivors included in the study by sex.

	Total	N	Females	N	Males	N
Sex (female/male, %)	42.2/57.8	116				
Age (years)	12.1 (3.3)	116	12.2 (3.5)	49	12.0 (3.2)	67
Body mass (kg)	46.6 (18.0)	116	45.2 (18.3)	49	47.6 (17.9)	67
Stature (cm)	147.5 (17.1)	116	145.3 (16.0)	49	149.0 (17.7)	67
Body mass index (kg/m^2)	20.7 (4.7)	116	20.7 (5.1)	49	20.7 (4.4)	67
Estimated years from peak height velocity	-0.8 (2.7)	116	0.0 (2.9)	49	-1.3 (2.5)	67
Time from treatment completion (years)	5.0 (3.8)	113	5.2 (4.1)	48	4.9 (3.6)	65
Radiotherapy exposure (yes/no, %)	27.6/72.4	116	24.5/75.5	49	29.8/70.2	67
Lean mass (kg)						
Total body less head	25.7 (10.4)	116	23.5 (8.5)	49	2.7 (1.1)	67
Legs	4.6 (2.0)	116	4.1 (1.6)	49	4.9 (2.1)	67
Trunk	14.3 (5.6)	116	13.4 (4.9)	49	15.0 (6.0)	67
aBMD Z-score						
Total body less head	-0.2 (1.4)	116	-0.2 (1.2)	49	-0.2 (1.5)	67
Total hip	0.1 (1.3)	115	0.2 (1.2)	48	0.1 (1.3)	67
Femoral neck	-0.2 (1.4)	115	0.1 (1.5)	48	-0.4 (1.3)	67
Lumbar spine	-0.1 (1.3)	116	-0.1 (1.2)	49	-0.1 (1.5)	67

Data are presented as mean (standard deviation) or as frequencies (percentages), as indicated. Areal bone mineral density (aBMD) Z-score parameters are presented using international reference data from the Bone Mineral Density in Childhood. Abbreviations: aBMD, areal bone mineral density.

Table S3. Distribution of cancer types of survivors included in this study.

	Total		Prepubertal		Peri/Post-pubertal	
	%	N	%	N	%	N
Acute lymphoblastic leukemia	38.8	45	41.4	24	36.2	21
Lymphoma	12.1	14	13.8	8	10.3	6
Central nervous system	9.5	11	5.2	3	13.8	8
Renal tumor	7.8	9	8.6	5	6.9	4
Neuroblastoma	6.9	8	12.1	7	1.7	1
Malignant bone tumor	6.9	8	3.5	2	10.3	6
Histiocytosis	5.2	6	5.2	3	5.2	3
Soft tissue and other extraosseous sarcomas	4.3	5	5.2	3	3.5	2
Retinoblastoma	3.4	4	1.7	1	5.2	3
Hepatic tumor	2.6	3	3.5	2	1.7	1
Other malignant epithelial neoplasms	1.7	2	0	0	3.5	2
Unknown	0.9	1	0	0	1.7	1

Chapter 8. Muscle strength deficits are associated with low bone mineral density in young paediatric cancer survivors: The iBoneFIT project

Abstract

Background. Paediatric cancer survivors are at increased risk of muscle weakness and low aBMD. However, the prevalence of muscle strength deficits is not well documented and the associations of muscle strength with aBMD are unknown in this population. Therefore, this study was aimed to investigate the prevalence of upper- and lower-body muscle strength deficits and to examine the associations of upper- and lower-body muscle strength with age-, sex- and race-specific aBMD Z-score at the total body, total hip, femoral neck and lumbar spine.

Methods. This cross-sectional study included 116 paediatric cancer survivors (12.1±3.3 years old; 42% female). Upper- and lower-body muscle strength were assessed by handgrip and standing long jump test, respectively. DXA was used to measure aBMD (g/cm^2). Associations between muscle strength and aBMD were evaluated in multivariable linear regression models. Logistic regression was used to evaluate the contribution of muscle strength (one-decile lower) to the odds of having low aBMD (Z-score less than -1.0). All analyses were adjusted for time from treatment completion, radiotherapy exposure and body mass index.

Results. More than half of survivors were within the two lowest deciles for upper- (56.9%) and lower- (60.0%) body muscle strength in comparison to age- and sex-specific reference values. Muscle strength deficits were associated with lower aBMD Z-score at all sites (B = 0.133 to 0.258, P = .001 to .032). Each one-decile lower in upper-body muscle strength was associated with higher odds of having low aBMD Z-score at all sites by 30%-95%. Each one-decile lower in lower-body muscle strength was associated with higher odds of having low aBMD Z-score at total body, total hip and femoral neck by 35%-70%.

Conclusion. Muscle strength deficits are prevalent in young paediatric cancer survivors and such deficits are associated with lower aBMD Z-score at all sites. These results suggest that interventions designed to improve muscle strength in this vulnerable population may have the added benefit of improving aBMD.

Introduction

Paediatric cancer survival has experienced a remarkable increase during the last decades [1], with a 5-year survivorship rate of 85% in children and 82% in adolescents [2]. However, paediatric cancer survivors are at risk of later health complications [3]. Low aBMD, defined by age-, sex- and race-specific aBMD Z- score less than -1.0, has been reported in up to two-thirds of survivors [4]. Paediatric cancer treatment includes DNA damaging agents and occurs during a critical period of active skeletal growth, interfering with accrual of bone mass [5-7]. This is shown by a decreased bone formation and increased bone resorption [8]. Chemotherapy and/or radiation not only interfere with bone metabolism, but also impact skeletal muscle mass [9] and function [10]. However, the prevalence of muscle strength deficits in young paediatric cancer survivors has not consistently been documented yet. In comparison to siblings, Hoffman et al. [11] identified preliminary lower-body muscle strength deficits in 183 young paediatric cancer survivors.

Muscle strength during childhood and adolescence is widely considered a powerful marker of health [12], and is strongly associated with higher aBMD during both adolescence [13] and later in life [14]. In healthy children and adolescents, measured upper- and lower-body muscle strength have been consistently associated with total body [15,16], upper [13,17] and lower [13,17] extremities BMC, and total body and femoral neck aBMD [18]. Likewise, in adult paediatric cancer survivors, Joyce et al. [19] found that upper- ($R^2 = 0.56$) and lower-body ($R^2 = 0.33$-0.40) muscle strength was positively associated with aBMD. However, in younger survivors, the literature describing associations of muscle strength with aBMD is scarce. Physical activity increases muscle strength during growth and according to the mechanostat theory of Frost HM [20], this creates the stimulus for bone to increase its mass. This is relevant since lower muscle strength after treatment completion could anticipate further decline in aBMD more exacerbated than in healthy population. Early detection of muscle strength deficits could help survivors, who lack cancer-related treatment exposures that trigger surveillance, to be screened for low aBMD. Currently, muscle strength deficits are not considered in paediatric cancer survivor screening guidelines as a risk factor for low aBMD [21,22].

Thus, the aims of this study were to: i) investigate the prevalence of upper- and lower-body muscle strength deficits in young paediatric cancer survivors compared to age- and sex-specific international reference data; and ii) to examine the associations of upper- and lower-body muscle strength with age-, sex- and race-specific aBMD Z-score at the total body, total hip, femoral neck and lumbar spine. We hypothesised that upper- and lower-body muscle strength

deficits would be prevalent in young paediatric cancer survivors. We also hypothesised that upper- and lower-body muscle strength deficits would be associated with low aBMD Z-score.

Methods

Study design and participants

This cross-sectional study included 116 paediatric cancer survivors (12.1±3.3 years old; 42% female) from the iBoneFIT project. A detailed description of the study protocol has been published elsewhere [23]. Briefly, iBoneFIT is a multicentre parallel group randomised controlled trial designed to examine the effect of a 9-month online exercise program on bone health in young paediatric cancer survivors. Survivors were recruited from the Units of Paediatric Oncology and Haematology of the 'Virgen de las Nieves' (Granada) and 'Reina Sofia' (Cordoba) University Hospitals. Inclusion criteria were aged from 6 to 18 years, not currently receiving treatments for cancer, diagnosed at least one year prior to enrolment and previous exposure to radiotherapy and/or chemotherapy. Data collection occurred in two waves due to COVID-19 restrictions: 1) October 2020 to February 2021; and 2) December 2021 to March 2022. All parents and survivors provided written informed consent and assent before entering the trial, respectively. The iBoneFIT project was approved by the Ethics Committee on Human Research of Regional Government of Andalusia (Reference: 4500, December 2019), followed the ethical guidelines of the Declaration of Helsinki (revised version 2013) and the randomised controlled trial was registered in isrctn.com (Reference: isrctn61195625, 2 April 2020). This study is reported according to the STROBE checklist (**Table S1**) [24]. Although we recruited 116 young paediatric cancer survivors in total, sample size slightly varies for some variables due to missing data (i.e., some survivors were unable to perform some of the tests, were afraid of being scanned using DXA or declined a particular test during their assessment).

Bone health

Survivors were evaluated using a single DXA scanner (Hologic Series Discovery QDR, Bedford, MA, USA) and analysed by APEX software (version 4.0.2). The device was calibrated each day using a lumbar spine phantom. Survivors were asked to remain still and scanned in the supine position according to the International Society of Clinical Densitometry [25]. Three regions were analysed (total body, right hip and lumbar spine) to characterise aBMD (g/cm^2) and BMC of the total body (less head), total hip, femoral neck and lumbar spine (mean of L1–L4). A single trained researcher analysed all DXA scans. According to the International Society of Clinical Densitometry [25], DXA assessment should be performed in children and

adolescents with disease that may affect the skeleton and when they may benefit from interventions to decrease their elevated risk of a clinically significant fracture. These are features of our sample as described in the literature [4]. DXA coefficient of variation in paediatric population ranges between 1.0 and 2.9%, depending on the region [26]. Moreover, using international reference data from the Bone Mineral Density in Childhood Study [27], age-, sex- and race-specific aBMD and BMC Z-score at the total body, total hip, femoral neck and lumbar spine were calculated for all the analyses.

Muscle strength

Upper-body muscle strength was evaluated using the handgrip test (TKK 5101 Grip D, Takei, Tokyo, Japan). Survivors, keeping the arm straight, squeezed the dynamometer during five seconds twice by each hand and the best score in kilograms were averaged. Handgrip test has shown good validity (intraclass correlation coefficients [ICC] 0.73 - 0.91) with high reproducibility and excellent test–retest reliability in children (ICC, 0.91 - 0.93) [28,29]. Lower-body muscle strength was assessed using the standing long jump test (considering motor coordination naturally occurring in human locomotion) which was performed twice after a short warmup, and the best score was retained in centimetres. This field-based test has demonstrated good validity (test with the strongest association with one maximum repetition, $P < .001$) and excellent test-retest reliability (ICC of 0.94) in children [30]. To get an appropriate insight into the status of muscle strength in our sample, performance on each test was compared with updated age- and sex-specific reference values of healthy young population based on nearly eight million test results from 34 countries gathered by the FitBack network [31]. Muscle strength deficits were identified as <2nd decile following previous reports showing sex-and age-specific percentiles definitions of fitness deficits created by Tomkinson et al. [32] and Ortega FB et al. [33].

Anthropometry and somatic maturity

Body mass (kg) was evaluated with an electronic scale (SECA 861, Hamburg, Germany) with an accuracy of 100 g. Stature (cm) was assessed using a precision stadiometer (SECA 225, Hamburg, Germany) to the nearest 0.1 cm. Body mass index was calculated as body mass (kg)/stature (m^2). Additionally, age- and sex-specific body mass index Z-score and categories were calculated using international reference data for paediatric population [34]. Somatic maturity was measured using the prediction of years before or after PHV using validated algorithms for boys and girls [35].

Clinical data and calcium

Medical record abstraction was used to retrieve diagnosis, time from treatment completion to baseline data collection and treatment exposures (radiotherapy, chemotherapy and/or surgery, alone or in combination). Diagnosis was not included in analysis as it was colinear with treatment exposure. Time from treatment completion was treated as a continuous variable and treatment exposure as a dichotomous variable, radiotherapy (yes/no). Finally, daily calcium (in milligrams) intake was estimated by a validated specific food-frequency questionnaire [(36)].

Total physical activity

The tri-axial ActiGraph wGT3x-BT accelerometers (ActiGraph GT3X, Pensacola, FL, USA) were used to measure total physical activity for seven consecutive days (24 hours/day). Young paediatric cancer survivors were instructed to wear devices always attached to the non-dominant wrist except for water activities. Accelerometers were initialised at a sampling frequency of 90 Hz and raw data were processed using the GGIR R open-source package version 2.8-2 [(37)]. Euclidean Norm of the raw acceleration minus one G with negative values rounded to zero (ENMO) was calculated, as well as the angle of the z-axis of the device to estimate physical activity and sleep parameters [(38)]. Non-wear time was detected based on the standard deviation of the raw accelerations recorded in the three accelerometer axes as described elsewhere [(39)], and then imputed by means of the acceleration in the rest of the days at the same time window. Appropriate thresholds were used to identify physical activity intensities (i.e., Moderate-to-vigorous physical activity: 200 mg and light physical activity: 35-200 mg) [(40)]. We considered a day valid when: 1) the accelerometer registered at least 23 hours/day and 2) survivors wore the accelerometers on at least 16 hours/day since in this study the accelerometers were worn at both day and night [(41)]. Survivors having at least one valid day were included (sensibility analyses showed similar results when compared to including participants having at least three valid weekdays and one weekend day). Total physical activity was calculated as the sum of daily average moderate-to-vigorous physical activity and light physical activity (mean of all seven days).

Statistical analyses

The normal distribution of the variables was checked and verified using skewness and kurtosis, Kolmogorov-Smirnov test, visual check of histograms, Q-Q and box plots. Descriptive data were reported as mean and SD or as frequencies (percentages). Multivariable linear regression

analyses were used to evaluate the associations of upper- and lower-body muscle strength with age-, sex- and race-specific aBMD Z-score at each site (same analyses were carried out for BMC Z-score). Models were created as follows: model 0 (no adjustments), model 1 (adjusted for time from treatment completion to baseline evaluation [years] and radiotherapy exposure [yes/no]), model 2 (adjusted for covariates in model 1 plus body mass index [kg/m^2]), model 3 (adjusted for covariates in model 2 plus calcium intake [mg]) and model 4 (adjusted for covariates in model 3 plus total physical activity [min/day]). To identify the minimum sufficient adjustment set (MSAS) for the associations of upper- and lower-body muscle strength with age-, sex- and race-specific aBMD and BMC Z-score, we built a theoretical causal diagram based on previous associations with muscle strength and/or aBMD and BMC available in the scientific literature [3,11,19,42-44]. We used the online tool DAGitty [45] to construct a directed acyclic graph (DAG) [46]. The covariates age, sex, time from treatment completion, radiotherapy exposure, body mass index, calcium intake and physical activity were identified as the MSAS (**Figure S1**). Radiotherapy exposure was the unique oncological treatment variable associated with aBMD and BMC (**Table S2**). Age and sex were already accounted using international reference data to calculate age-, sex- and race-specific aBMD and BMC Z-score. Binary logistic regression was used to evaluate the contribution of muscle strength (one-decile lower) to the odds of having low aBMD (Z-score less than -1.0 [4]). Same analyses were conducted for BMC Z-score. Results are presented as odds ratios (ORs) with 95%CIs. Similar models were built for logistic regressions. Statistical analyses were performed using the statistical software R version 4.0.3 (R Foundation for Statistical Computing), B coefficient was presented non-standardised and P-values < .05 were considered statistically significant.

Results

Among 196 young paediatric cancer survivors initially screened for participation, 116 were enrolled and included in this study (**Figure S2**).

Participant characteristics

Descriptive characteristics of our sample are presented in **Table 1**. The average age (and standard deviation) of the total sample was 12.1 (3.3) years and 42.2% were female. The majority of survivors were diagnosed with acute lymphoblastic leukaemia (38.8%), lymphoma (12.1%) and central nervous system tumours (9.5%). **Table 2** shows that more than half of survivors had muscle strength deficits (upper- [56.9%] and lower- [60.0%] body muscle strength deciles). Regarding bone health (**Table 2**), the average of total body aBMD Z-score

was -0.2 (1.4) and BMC Z-score -0.5 (1.3), total hip aBMD Z-score was 0.1 (1.3) and BMC Z-score 0.4 (1.4), femoral neck aBMD Z-score was -0.2 (1.4) and BMC Z-score -1.3 (1.5), and lumbar spine aBMD Z-score was -0.1 (1.3) and BMC Z-score -0.5 (1.3). Participant characteristics by childhood cancer diagnosis (soft/solid tumours) are presented in **Table S3**.

Associations of muscle strength with aBMD Z-score at each site

All associations of upper- and lower-body muscle strength with aBMD Z-score at the total body, total hip, femoral neck and lumbar spine examined by multivariable linear regression are shown in Fig. 1. We observed that upper-body muscle strength deficits were associated with lower aBMD Z-score at total body (B = 0.258, 95% CI: 0.169-0.346, P < .001), total hip (B = 0.208, 0.116-0.301, P < .001), femoral neck (B = 0.175, 0.076-0.275, P < .001) and lumbar spine (B = 0.194, 0.095-0.294, P < .001). Concerning lower-body muscle strength deficits, we found significant associations with lower aBMD Z-score at total body (B = 0.183, 95% CI: 0.068-0.298, P = .002), total hip (B = 0.160, 0.045-0.275, P = .007), femoral neck (B = 0.133, 0.011-0.254, P = .032) and lumbar spine (B = 0.153, 0.031-0.275, P = .014). After adjusting for calcium intake (mg) and total physical activity (min/day), results were mostly similar (**Tables S4-5**). Likewise, when examining same analyses for BMC Z-score, results were considerably consistent (**Figure S3** and **Tables S6-7**).

Odds ratios of low aBMD Z-score at each site

The risk of low aBMD Z-score associated with one-decile lower in upper- and lower-body muscle strength is presented in Fig. 2. Each one-decile lower in upper-body muscle strength was associated with higher odds of having aBMD Z-score less than -1.0 at the total body (OR: 1.95, 95% CI: 1.38-3.11), total hip (OR: 1.36, 1.04-1.95), femoral neck (OR: 1.31, 1.04-1.74) and lumbar spine (OR: 1.30, 1.03-1.73). Regarding lower-body muscle strength, each one-decile lower was associated with higher odds of having aBMD Z-score less than -1.0 at the total body (OR: 1.36, 95% CI: 1.05-1.87), total hip (OR: 1.70, 1.15-2.92) and femoral neck (OR: 1.35, 1.03-1.89). These results did not change after controlling for calcium intake (mg) and total physical activity (min/day) (**Table S8**). Similarly, findings were mainly consistent when examining same analyses for BMC Z-score (**Figure S4** and **Table S8**).

Table 1. Descriptive characteristics of the survivors included in the study.

Characteristic	Total	N	Females	N	Males	N
Sex (female/male, %)	42.2/57.8	116				
Age (years)	12.1 (3.3)	116	12.2 (3.5)	49	12.0 (3.2)	67
Body mass (kg)	46.6 (18.0)	116	45.2 (18.3)	49	47.6 (17.9)	67
Stature (cm)	147.5 (17.1)	116	145.3 (16.0)	49	149.0 (17.7)	67
Body mass index Z-score	0.9 (1.1)	116	0.8 (1.1)	49	1.0 (1.2)	67
Body mass index (categories, %)						
Underweight	3.5	4	6.1	3	1.5	1
Normoweight	61.2	71	65.4	32	58.2	39
Overweight	20.7	24	16.3	8	23.9	16
Obese	14.6	17	12.2	6	16.4	11
Years from peak height velocity	-0.8 (2.7)	116	0.0 (2.9)	49	-1.3 (2.5)	67
Time from treatment completion (years)	5.0 (3.8)	113	5.2 (4.1)	48	4.9 (3.6)	65
Radiotherapy exposure (yes/no, %)	27.6/72.4	116	24.5/75.5	49	29.8/70.2	67
Cancer type						
Acute lymphoblastic leukaemia	38.8	45	36.7	18	40.3	27
Lymphoma	12.1	14	12.2	6	11.9	8
Central nervous system tumours	9.5	11	10.2	5	9.0	6
Renal tumours	7.8	9	4.1	2	10.5	7
Neuroblastoma	6.9	8	12.2	6	3.0	2
Malignant bone tumours	6.9	8	8.2	4	6.0	4
Histiocytosis	5.2	6	6.1	3	4.5	3
Soft tissue and other extraosseous sarcomas	4.3	5	0.0	0	7.5	5
Retinoblastoma	3.5	4	4.1	2	3.0	2
Hepatic tumours	2.6	3	4.1	2	1.5	1
Other malignant epithelial neoplasms	1.7	2	2.0	1	1.5	1
Unspecified malignant neoplasms	0.9	1	0.0	0	1.5	1

Data are presented as mean (standard deviation) or as frequencies (percentages), as indicated.

Table 2. Distribution of upper- and lower-body muscle strength deciles and age-, sex- and race-specific areal bone mineral density (aBMD) and bone mineral content (BMC) Z-score.

Characteristic	Total	N	Females	N	Males	N
Muscle strength						
Upper-body reference deciles (%)						
1	32.8	38	32.7	16	32.8	22
2	24.1	28	26.5	13	22.4	15
3	12.1	14	12.2	6	11.9	8
4	6.0	7	6.1	3	6.0	4
5	5.2	6	6.1	3	4.5	3
6	7.8	9	8.2	4	7.5	5
7	6.9	8	4.2	2	8.9	6
8	2.6	3	2.0	1	3.0	2
9	1.6	2	0	0	3.0	2
10	0.9	1	2.0	1	0	0
Lower-body reference deciles (%)						
1	40.9	47	40.8	20	40.9	27
2	19.1	22	22.5	11	16.7	11
3	9.6	11	6.1	3	12.1	8
4	12.2	14	18.4	9	7.6	5
5	7.0	8	6.2	3	7.6	5
6	5.2	6	2.0	1	7.6	5
7	2.6	3	2.0	1	3.0	2
8	0.9	1	0	0	1.5	1
9	1.7	2	0	0	3.0	2
10	0.9	1	2.0	1	0	0
aBMD Z-score						
Total body (less head)	-0.2 (1.4)	116	-0.2 (1.2)	49	-0.2 (1.5)	67
Total hip	0.1 (1.3)	115	0.2 (1.2)	48	0.1 (1.3)	67
Femoral neck	-0.2 (1.4)	115	0.1 (1.5)	48	-0.4 (1.3)	67
Lumbar spine	-0.1 (1.3)	116	-0.1 (1.2)	49	-0.1 (1.5)	67
BMC Z-score						
Total body (less head)	-0.5 (1.3)	116	-0.5 (1.1)	49	-0.5 (1.4)	67
Total hip	0.4 (1.4)	115	0.3 (1.2)	48	0.5 (1.6)	67
Femoral neck	-1.3 (1.5)	115	-1.4 (1.5)	48	-1.2 (1.5)	67
Lumbar spine	-0.5 (1.3)	116	-0.4 (1.1)	49	-0.5 (1.4)	67

Data are presented as mean (standard deviation) or as frequencies (percentages), as indicated. Upper- and lower-body muscle strength reference deciles are shown using FitBack reference values. Age-, sex- and race-specific aBMD and BMC Z-score at each site are presented using international reference data from the Bone Mineral Density in Childhood Study.

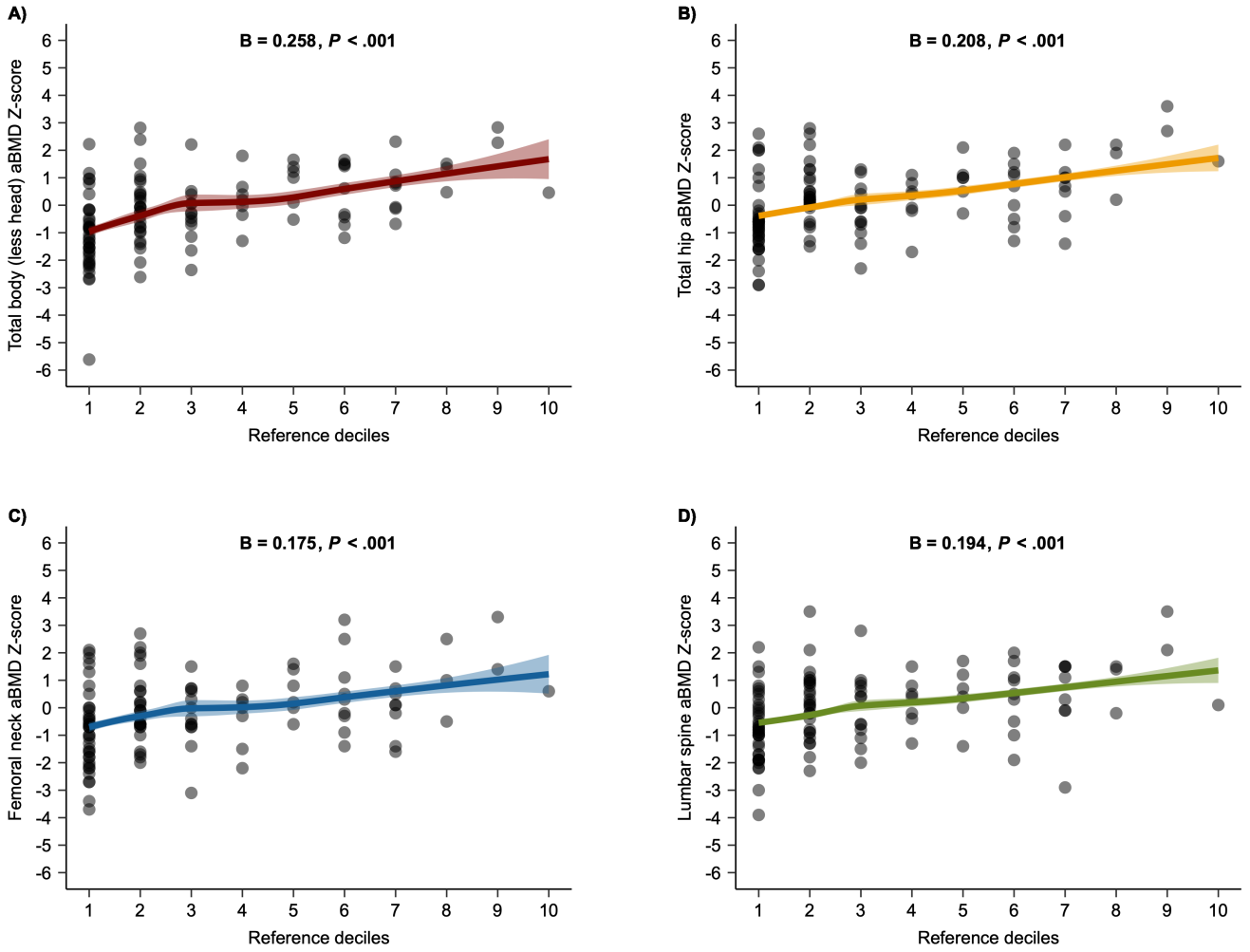

Figure 1. Associations of upper-body muscle strength (Reference deciles using FitBack reference values) with age-, sex-, and race-specific areal bone mineral density (aBMD) Z-score at each site. Multivariable linear regression models were adjusted for time from treatment completion (years), radiotherapy exposure (yes/no) and body mass index. Age-, sex-, and race-specific aBMD Z-score at each site is presented using international reference data from the Bone Mineral Density in Childhood Study [(27)].

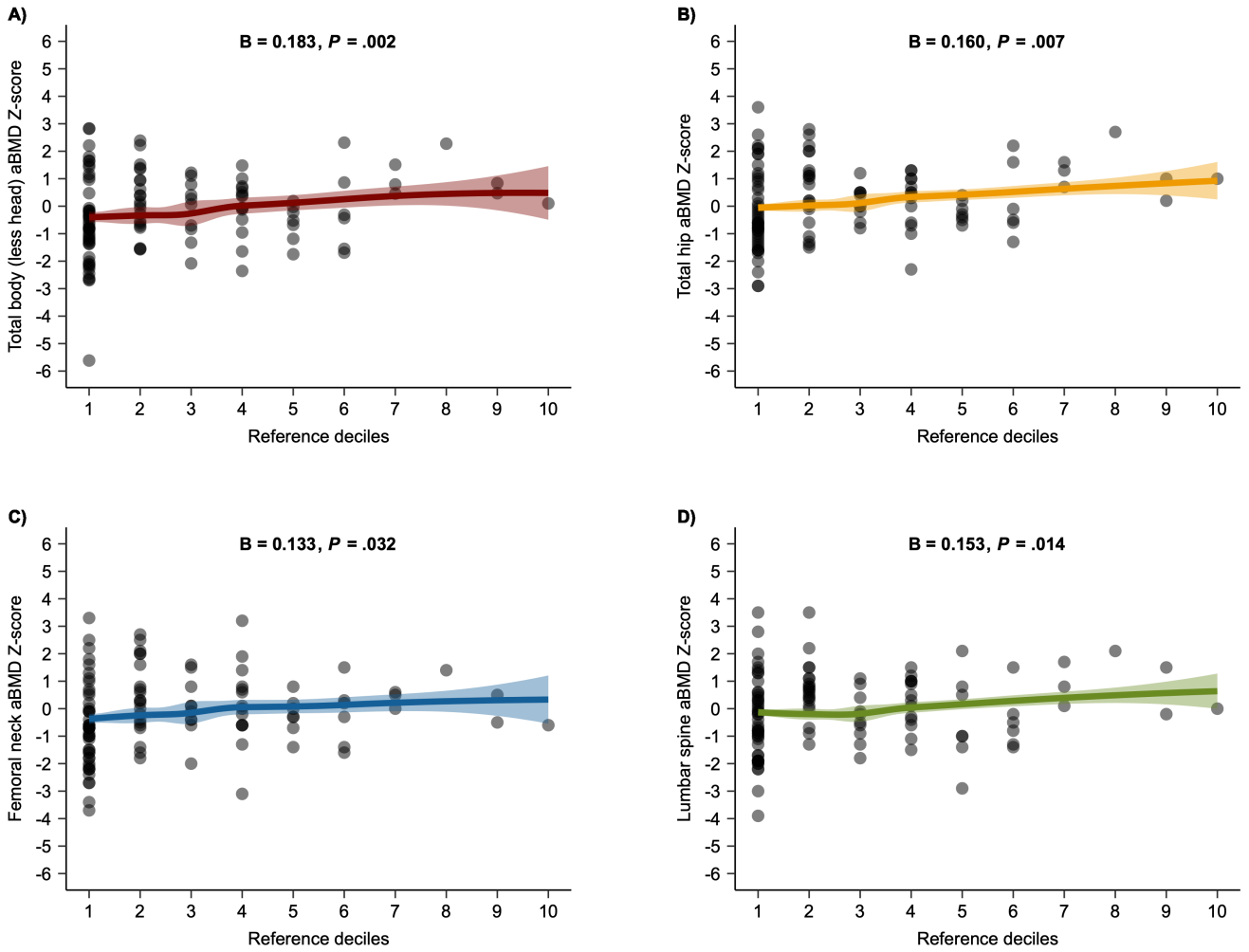

Figure 2. Associations of lower-body muscle strength (Reference deciles using FitBack reference values) with age-, sex-, and race-specific areal bone mineral density (aBMD) Z-score at each site. Multivariable linear regression models were adjusted for time from treatment completion (years), radiotherapy exposure (yes/no) and body mass index. Age-, sex-, and race-specific aBMD Z-score at each site is presented using international reference data from the Bone Mineral Density in Childhood Study [27].

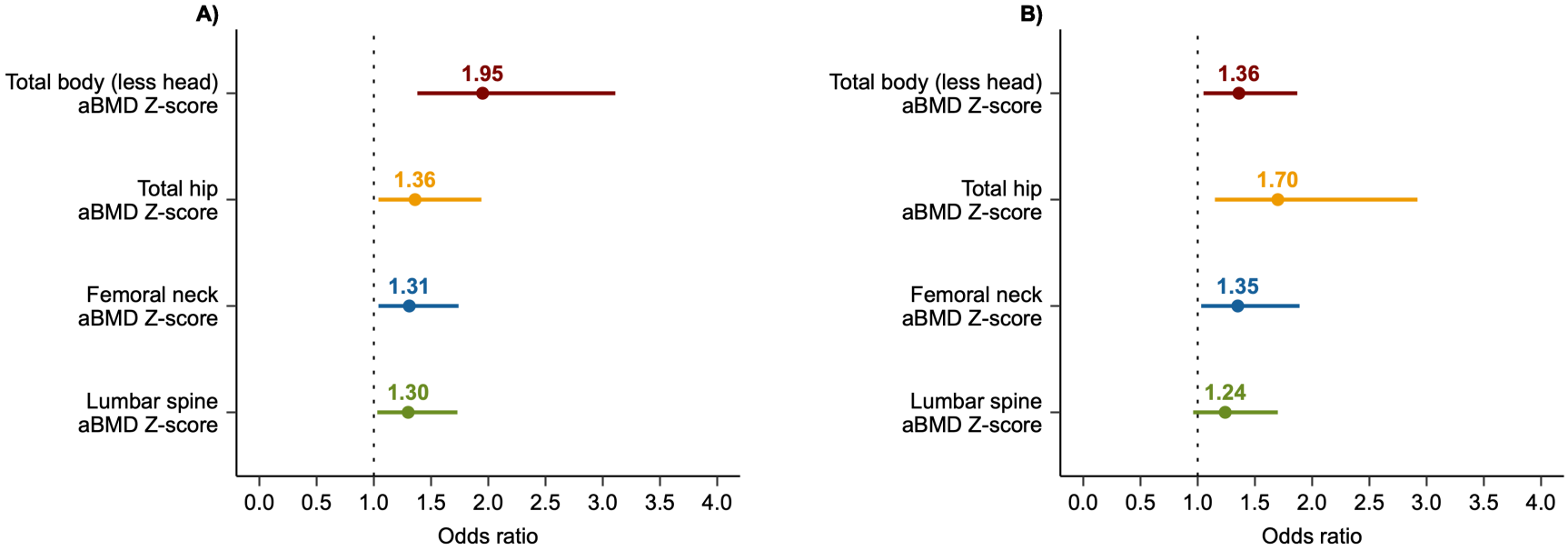

Figure 3. Odds ratios of low age-, sex-, and race-specific areal bone mineral density (aBMD) Z-score at each site per one-decile lower in upper- (A) and lower-body (B) muscle strength (Reference deciles using FitBack reference values). Binary logistic regression (low aBMD identified as Z-score less than–1.0, according to according to van Atteveld et al. [4] and normal aBMD identified as Z-score higher than–1.0) was used to estimate odds ratios with 95% confidence intervals. Adjusted models included time from treatment completion (years), radiotherapy exposure (yes/no) and body mass index. Age-, sex-, and race-specific aBMD Z-score at each site is presented using international reference data from the Bone Mineral Density in Childhood Study [27].

Discussion

More than half of young paediatric cancer survivors, enrolled on a clinical trial to improve bone health, had upper- and lower-body muscle strength deficits when compared to geographically diverse updated age- and sex-specific reference values [31]. Importantly, we found that muscle strength deficits were consistently associated with lower aBMD Z-score at the total body, total hip, femoral neck and lumbar spine [27]. Each one-decile lower in muscle strength was associated with higher odds of having low aBMD Z-score by 30%-95%. These results suggest that interventions designed to improve muscle strength in paediatric cancer survivors may have the potential benefit of improving aBMD.

The literature describing associations of muscle strength with aBMD in young paediatric cancer survivors is scarce. Objectively measured upper- and lower-body muscle strength have been strongly associated with total body [15,16], upper [13,17] and lower [13,17] extremities BMC, and total body and femoral neck aBMD [18], in healthy children and adolescents. Our results indicate that these associations could be even stronger in young paediatric cancer survivors (6 to 18 years old) and may never recover. Previous data from Joyce et al. [19] where muscle strength deficits and aBMD were positively correlated among 493 adult survivors of paediatric onset acute lymphoblastic leukaemia (33.3 ± 7.1 years old), suggest that loss of muscle strength early in life may precipitate further decline in aBMD.

Our findings of the associations of upper-body muscle strength with aBMD at multiple sites are consistent with data from reports among healthy children and adolescents. Vicente-Rodriguez et al. [15] reported that upper-body muscle strength was consistently the strongest fitness variable which positively correlated with total body BMC in 278 adolescents (13.0 to 18.5 years old); Gracia-Marco et al. [13] showed that among 234 non-active adolescents (14.8 ± 1.2 years old), those with reduced upper-body muscle strength had also lower BMC at total body and upper extremities; Saint-Maurice et al. [16] reported positive associations between upper-body muscle strength and height-adjusted total BMC in 433 children and adolescents (14.1 ± 2.3 years old); and Wang et al. [17] reported positive correlations between maximal voluntary contraction of the elbow flexors and upper extremity BMC among 258 pubertal girls (11.2, 9.8 to 12.6 years old).

Our findings of the associations of lower-body muscle strength with aBMD are not completely consistent with previous findings in healthy young population since lower-body lean mass seemed to be a better predictor of aBMD than muscle strength [47]. This could be because the lower extremities are subject to higher mechanical loadings than the upper extremities, with more opportunity for bone regeneration and formation [48], or because our

measure of lower-body strength required not only strength, but also balance and coordination. Nevertheless, our lower-body muscle strength and aBMD results are consistent with results in non-cancer populations. Baptista et al. [18] evaluated 114 healthy younger children (8.5 ± 0.4 years old), and found positive associations between lower-body muscle strength (vertical jump test) and height-adjusted total body and femoral neck aBMD; Gracia-Marco et al. [13] evaluated non-active adolescents, and found that those with reduced lower-body muscle strength (standing long jump test) presented decreased BMC at total body and lower extremities; and Wang et al. [17] evaluated pubertal girls (11.2, 9.8 to 12.6 years old), and found that maximal isometric voluntary extension of the left knee was positively correlated with lower extremity BMC. Altogether, our findings could be explained by the functional muscle bone unit [49], based on the mechanostat theory of Frost HM [20], which predicts that the increasing muscle strength during growth creates the stimulus for bone to increase its mass. Given the high risk of muscle strength deficits and low aBMD Z-score in young paediatric cancer survivors, these associations are mostly stronger in comparison to the previously mentioned studies in healthy children and adolescents.

Limitations

Our study results should be considered in the context of some potential limitations. First, the cross-sectional design does not allow us to examine the temporal associations between reduced muscle strength and aBMD. Second, included survivors were those who elected to enroll in an exercise intervention to improve aBMD. They may not be representative of all young paediatric cancer survivors, making our prevalence estimates particularly vulnerable to selection bias. Third, although we adjusted the analyses for some major potential confounders identified through the DAG method (i.e., age, sex, time from treatment completion, radiotherapy exposure, body mass index, physical activity and calcium intake), residual confounding cannot be eliminated. Fourth, given that bone depth is not factored into DXA results, reliance on aBMD systematically may underestimate bone density in shorter individuals. Fifth, although standing long jump has been shown to be valid and reliable in children, other tests might be more appropriate to assess specifically muscle strength.

Public health implications

Previous literature has documented preliminary lower-body muscle strength deficits and low aBMD Z-score in young paediatric cancer survivors. However, our study indicates that not only lower- but also upper-body muscle strength deficits are prevalent and associated with low

aBMD soon after the treatment completion, even among survivors without known risk factors for low aBMD. For instance, for a ten-year-old girl performing 7.3 kg in the handgrip strength test - within decile one using FitBack reference values - her aBMD Z-score is -2.2, which is considered low aBMD. However, a girl of the same age performing 16.8 kg in the same test - within decile six - the aBMD Z-score is 1.4, which is not considered low aBMD. Our data indicate that children and adolescents who present muscle strength deficits should be screened for low aBMD and suggest that interventions to improve muscle strength could also improve aBMD [50]. However, a very recent meta-analysis has found that previous interventions aimed at improving muscle strength and/or aBMD were inappropriate (i.e., performed in microgravity environments such as swimming pools [51], short durations of three months [50,51], types of exercises not including weight-bearing impact exercises of high intensity [52]) and hence, ineffective to illustrate any beneficial effect in this population [53]. These findings warrant further research.

Conclusion

In a sample of young paediatric cancer survivors who electively enrolled on an intervention study to improve bone health, this study identified both upper- and lower-body muscle strength deficits and associations of such deficits with lower aBMD. Further research in cohort studies is needed to validate these findings so they can be incorporated into surveillance guidelines and provide a foundation for individualised exercise-oncology plans development, specifically adapted to the needs of the patients.

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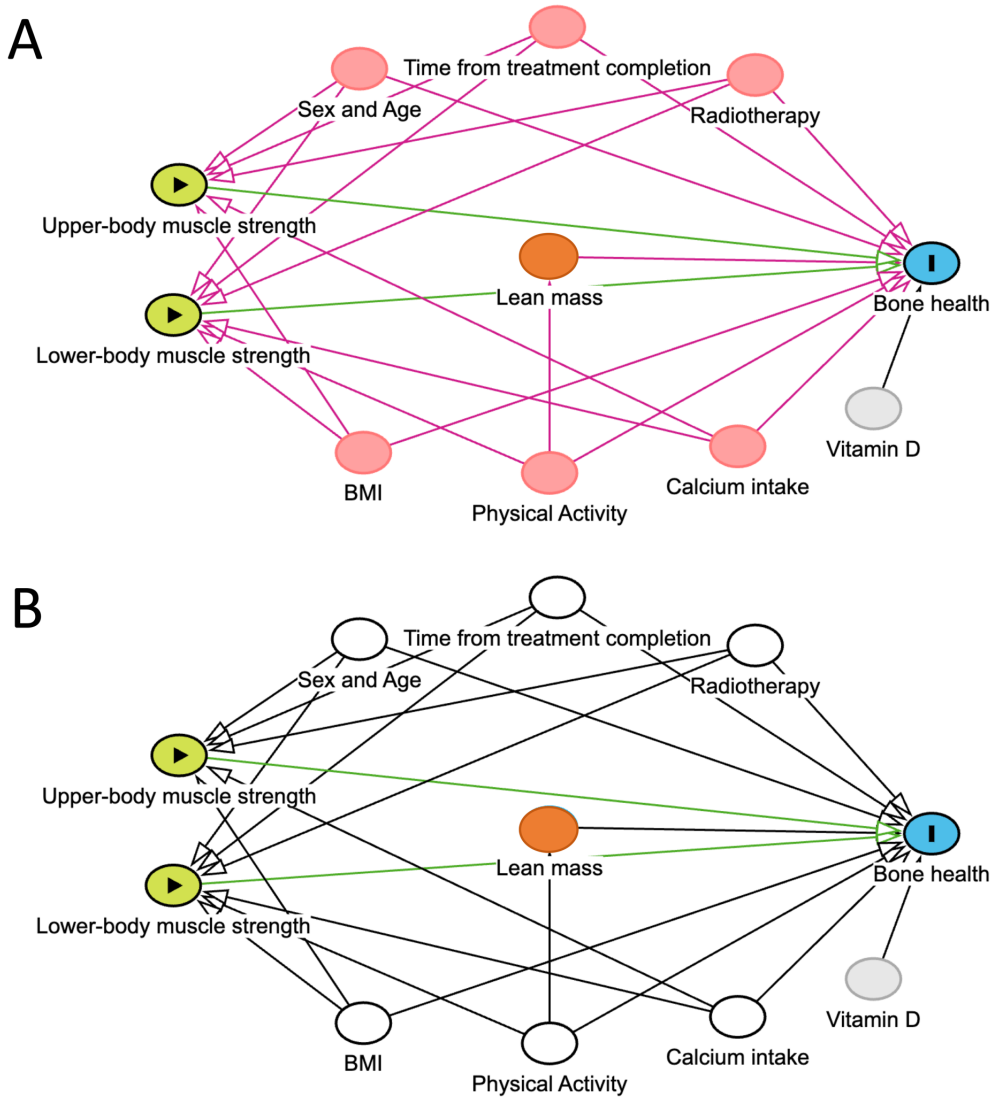

Figure S1. Directed acyclic graph (DAG).

Panel A represents the DAG for the causal structure of the relationship between upper- and lower-muscle strength (exposure, green circle) and bone health (outcome, blue circle). Pink circles indicate ancestor variables of both the exposure and the outcome (sex, age, time from treatment completion, radiotherapy exposure, body mass index (BMI), physical activity and calcium intake). Orange circles indicate ancestor variables of the outcome (lean mass). Green arrows indicate "causal" paths, and pink arrows indicate biasing paths.

Panel B represent the DAG after adjusting for the minimum sufficient adjustment set for the total effect (i.e., sex, age, time from treatment completion, radiotherapy exposure, body mass index, physical activity and calcium intake, now represented with white circles). Note that the biasing paths were completely closed (pink arrows became black arrows, suggesting the correct control for the relevant confounders), and that only the "causal" paths remained opened (both the direct path and the indirect paths, i.e., through mediators).

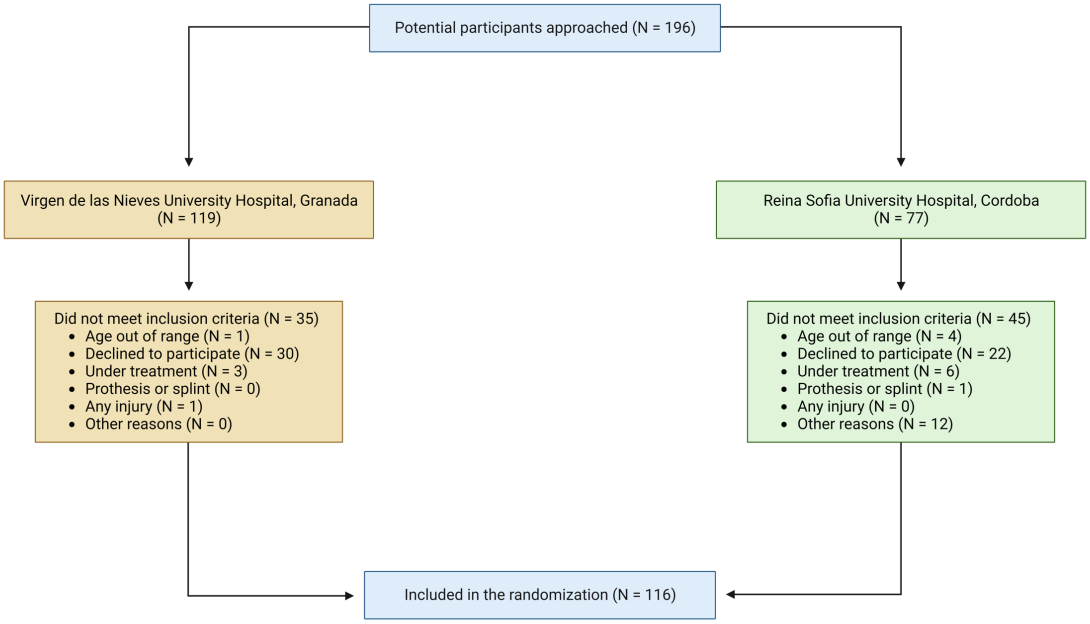

Figure S2. Flow chart.

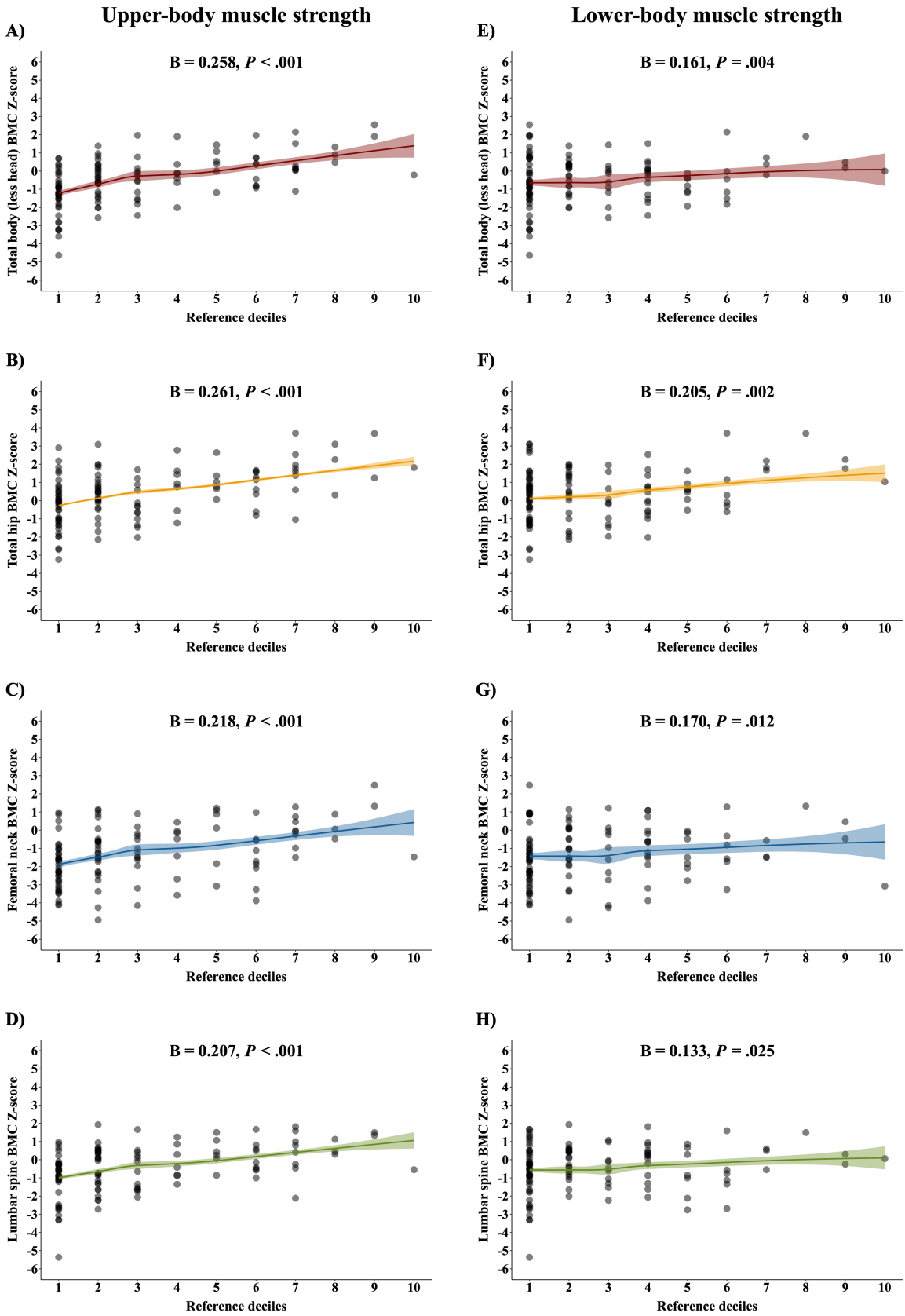

Figure S3. Associations of upper-body muscle strength (Panels A-D) and lower-body muscle strength (Panels E-H) (Reference deciles using FitBack reference values) with age-, sex- and race-specific bone mineral content (BMC) Z-score at each site. Multivariable linear regression models were adjusted for time from treatment completion (years), radiotherapy exposure (yes/no) and body mass index. Age-, sex- and race-specific BMC Z-score at each site is presented using international reference data from the Bone Mineral Density in Childhood Study [(1)].

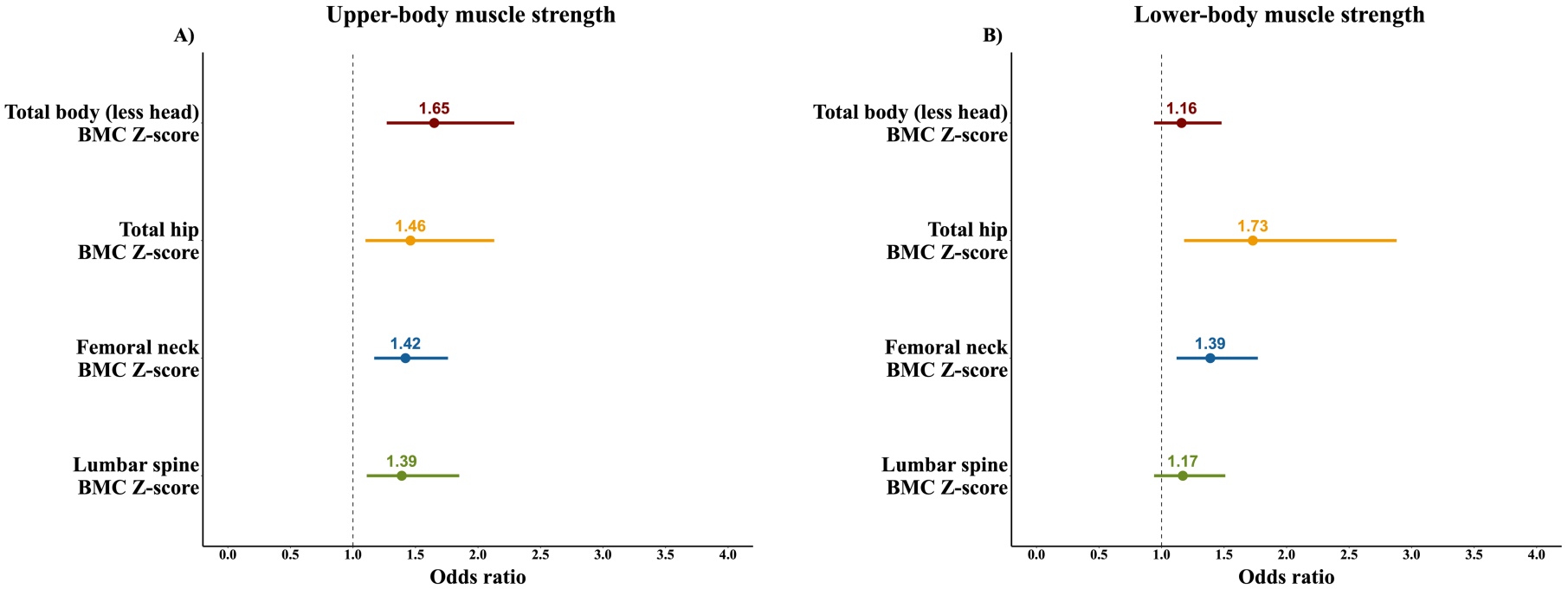

Figure S4. Odds ratios of low age-, sex- and race-specific bone mineral content (BMC) Z-score at each site per one-decile lower in upper-body and lower-body muscle strength (Reference deciles using FitBack reference values). Binary logistic regression (low BMC identified as Z-score less than -1.0, and normal BMC identified as Z-score higher than -1.0) was used to estimate odds ratios with 95% confidence intervals. Adjusted models included time from treatment completion (years), radiotherapy exposure (yes/no) and body mass index. Age-, sex- and race-specific BMC Z-score at each site is presented using international reference data from the Bone Mineral Density in Childhood Study [1].

Table S1. STROBE Statement-Checklist of items that should be included in reports of *cross-sectional studies.*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	176
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	176
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	177-178
Objectives	3	State specific objectives, including any prespecified hypotheses	177-178
Methods			
Study design	4	Present key elements of study design early in the paper	178
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	178
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	178
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	178-180
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	178-180
Bias	9	Describe any efforts to address potential sources of bias	180-181
Study size	10	Explain how the study size was arrived at	178
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	178-180
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	180-181
		(*b*) Describe any methods used to examine subgroups and interactions	180-181
		(*c*) Explain how missing data were addressed	180-181

		(*d*) If applicable, describe analytical methods taking account of sampling strategy	180-181
		(*e*) Describe any sensitivity analyses	180-181
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure S2
		(b) Give reasons for non-participation at each stage	Figure S2
		(c) Consider use of a flow diagram	Figure S2
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, Tables S2-3 and Figure S1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1 and Tables S2-3
Outcome data	15	Report numbers of outcome events or summary measures	Table 2, Tables S4-8, Figures 1-3 and Figures S3-4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figures 1-3 and Figures S3-4
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	181-182
Discussion			
Key results	18	Summarise key results with reference to study objectives	188
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	189
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	188-190
Generalisability	21	Discuss the generalisability (external validity) of the study results	189-190

Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

Note: An explanation and elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Table S2. Univariate linear regression for the associations of oncological treatment (chemotherapy exposure, surgery and radiotherapy exposure) and age-, sex- and race-specific areal bone mineral density (aBMD) and bone mineral content (BMC) Z-score at each site in young paediatric cancer survivors.

		B	95% CI	Adj. R^2	f^2	*P*	N
Total body (less head) aBMD Z-score	Chemotherapy exposure	0.859	(-0.804, 2.522)	0.087	0.095	.308	113
	Surgery	0.015	(-0.565, 0.595)	0.087	0.095	.959	46
	Radiotherapy exposure	-0.918	(-1.586, -0.250)	0.087	0.095	.008	30
Total hip aBMD Z-score	Chemotherapy exposure	0.975	(-0.638, 2.588)	0.020	0.020	.234	112
	Surgery	-0.088	(-0.657, 0.482)	0.020	0.020	.761	45
	Radiotherapy exposure	-0.395	(-1.047, 0.258)	0.020	0.020	.233	30
Femoral neck aBMD Z-score	Chemotherapy exposure	0.967	(-0.739, 2.673)	0.061	0.065	.264	112
	Surgery	-0.105	(-0.707, 0.497)	0.061	0.065	.731	45
	Radiotherapy exposure	-0.718	(-1.408, -0.028)	0.061	0.065	.042	30
Lumbar spine aBMD Z-score	Chemotherapy exposure	1.544	(-0.118, 3.206)	0.038	0.040	.068	113
	Surgery	0.362	(-0.218, 0.941)	0.038	0.040	.219	46
	Radiotherapy exposure	-0.246	(-0.913, 0.422)	0.038	0.040	.467	30
Total body (less head) BMC Z-score	Chemotherapy exposure	1.369	(-0.204, 2.941)	0.072	0.078	.087	113
	Surgery	0.005	(-0.543, 0.553)	0.072	0.078	.986	46
	Radiotherapy exposure	-0.644	(-1.275, -0.012)	0.072	0.078	.046	30
Total hip BMC Z-score	Chemotherapy exposure	0.948	(-0.836, 2.732)	0.005	0.005	.295	112
	Surgery	-0.191	(-0.821, 0.439)	0.005	0.005	.549	45
	Radiotherapy exposure	-0.274	(-0.996, 0.448)	0.005	0.005	.453	30
Femoral neck BMC Z-score	Chemotherapy exposure	0.444	(-1.446, 2.334)	0.019	0.019	.642	112
	Surgery	-0.256	(-0.923, 0.411)	0.019	0.019	.449	45
	Radiotherapy exposure	-0.500	(-1.264, 0.265)	0.019	0.019	.198	30
Lumbar spine BMC Z-score	Chemotherapy exposure	0.190	(-0.008, 0.387)	0.038	0.040	.059	113
	Surgery	0.008	(-0.204, 0.220)	0.038	0.040	.943	46
	Radiotherapy exposure	-0.122	(-0.340, 0.097)	0.038	0.040	.273	30

Univariate linear regression analyses between chemotherapy exposure (yes/no), surgery (yes/no) and radiotherapy exposure (yes/no) and, aBMD and BMC Z-score at each site (presented using international reference data from the Bone Mineral Density in Childhood Study [1]. The criteria of f^2 statistic for small, medium, and large effect are 0.02, 0.15, and 0.35, respectively [2].

Table S3. Distribution of upper- and lower-body muscle strength deciles, and age-, sex- and race-specific areal bone mineral density (aBMD) and bone mineral content (BMC) Z-score at each site in young paediatric cancer survivors.

Characteristic	Total	N	Soft tumours	N	Solid tumours	N
Muscle strength						
Upper-body reference deciles (%)						
1	32.8	38	28.6	20	37.8	17
2	24.1	28	25.7	18	22.2	10
3	12.1	14	14.3	10	8.9	4
4	6.0	7	4.3	3	8.9	4
5	5.2	6	4.3	3	6.7	3
6	7.8	9	10.0	7	4.4	2
7	6.9	8	8.6	6	4.4	2
8	2.6	3	2.9	2	2.2	1
9	1.6	2	0.0	0	4.4	2
10	0.9	1	1.4	1	0.0	0
Lower-body reference deciles (%)						
1	40.9	47	43.5	30	37.8	17
2	19.1	22	18.8	13	20.0	9
3	9.6	11	10.1	7	8.9	4
4	12.2	14	13.0	9	8.9	4
5	7.0	8	4.3	3	11.1	5
6	5.2	6	5.8	4	4.4	2
7	2.6	3	2.9	2	2.2	1
8	0.9	1	0.0	0	2.2	1
9	1.7	2	1.4	1	2.2	1
10	0.9	1	0.0	0	2.2	1
aBMD Z-score						
Total body (less head)	-0.2 (1.4)	116	-0.2 (1.4)	70	-0.1 (1.4)	45
Total hip	0.1 (1.3)	115	0.0 (1.2)	69	0.4 (1.4)	45
Femoral neck	-0.2 (1.4)	115	-0.3 (1.3)	69	0.0 (1.5)	45
Lumbar spine	-0.1 (1.3)	116	-0.2 (1.2)	70	0.2 (1.5)	45
BMC Z-score						
Total body (less head)	-0.5 (1.3)	116	-0.5 (1.3)	70	-0.5 (1.4)	45
Total hip	0.4 (1.4)	115	0.5 (1.5)	69	0.4 (1.3)	45
Femoral neck	-1.3 (1.5)	115	-1.2 (1.5)	69	-1.3 (1.6)	45
Lumbar spine	-0.5 (1.3)	116	-0.5 (1.3)	70	-0.3 (1.3)	45

Data are presented as mean (standard deviation) or as frequencies (percentages), as indicated. Upper- and lower-body muscle strength reference deciles are shown using FitBack reference values. Age-, sex- and race-specific aBMD and BMC Z-score at each site are presented using international reference data from the Bone Mineral Density in Childhood Study [(1)].

Table S4. Multiple lineal regressions for the associations of upper-body muscle strength with age-, sex- and race-specific areal bone mineral density (aBMD) Z-score at each site in young paediatric cancer survivors.

			B	95% CI	Adj. R^2	f^2	*P*	N
Total body (less head) aBMD Z-score	Model 0	Intercept	-1.065	(-1.437, -0.692)	0.222	0.285	.001	116
	Model 0	Upper-body muscle strength	0.285	(0.188, 0.382)	0.222	0.285	.001	116
	Model 1	Intercept	-0.859	(-1.362, -0.355)	0.294	0.416	.001	113
	Model 1	Upper-body muscle strength	0.277	(0.183, 0.371)	0.294	0.416	.001	113
	Model 1	Time from treatment completion	0.003	(-0.055, 0.061)	0.294	0.416	.915	113
	Model 1	Radiotherapy exposure	-0.831	(-1.331, -0.330)	0.294	0.416	.001	113
	Model 2	Intercept	-2.595	(-3.564, -1.626)	0.382	0.618	.001	113
	Model 2	Upper-body muscle strength	0.258	(0.169, 0.346)	0.382	0.618	.001	113
	Model 2	Time from treatment completion	-0.023	(-0.079, 0.033)	0.382	0.618	.412	113
	Model 2	Radiotherapy exposure	-0.808	(-1.277, -0.340)	0.382	0.618	.001	113
	Model 2	Body mass index	0.093	(0.047, 0.138)	0.382	0.618	.000	113
	Model 3	Intercept	-2.616	(-3.741, -1.491)	0.376	0.603	.001	113
	Model 3	Upper-body muscle strength	0.258	(0.169, 0.347)	0.376	0.603	.001	113
	Model 3	Time from treatment completion	-0.023	(-0.080, 0.033)	0.376	0.603	.418	113
	Model 3	Radiotherapy exposure	-0.809	(-1.279, -0.338)	0.376	0.603	.001	113
	Model 3	Body mass index	0.093	(0.047, 0.139)	0.376	0.603	.000	113
	Model 3	Calcium intake	0.000	(0.000, 0.000)	0.376	0.603	.942	113
	Model 4	Intercept	-3.962	(-5.395, -2.528)	0.415	0.710	.001	108
	Model 4	Upper-body muscle strength	0.226	(0.133, 0.319)	0.415	0.710	.001	108
	Model 4	Time from treatment completion	-0.017	(-0.074, 0.039)	0.415	0.710	.549	108
	Model 4	Radiotherapy exposure	-0.689	(-1.185, -0.193)	0.415	0.710	.007	108
	Model 4	Body mass index	0.107	(0.061, 0.153)	0.415	0.710	.001	108
	Model 4	Calcium intake	0.000	(0.000, 0.000)	0.415	0.710	.926	108
	Model 4	Total physical activity	0.004	(0.001, 0.006)	0.415	0.710	.008	108
Total hip aBMD Z-score	Model 0	Intercept	-0.550	(-0.915, -0.186)	0.156	0.184	.003	115
	Model 0	Upper-body muscle strength	0.224	(0.130, 0.319)	0.156	0.184	.001	115
	Model 1	Intercept	-0.678	(-1.180, -0.176)	0.189	0.232	.009	112
	Model 1	Upper-body muscle strength	0.223	(0.129, 0.317)	0.189	0.232	.001	112
	Model 1	Time from treatment completion	0.042	(-0.017, 0.101)	0.189	0.232	.166	112
	Model 1	Radiotherapy exposure	-0.354	(-0.854, 0.145)	0.189	0.232	.162	112
	Model 2	Intercept	-1.866	(-2.910, -0.822)	0.228	0.295	.001	112
	Model 2	Upper-body muscle strength	0.208	(0.116, 0.301)	0.228	0.295	.001	112
	Model 2	Time from treatment completion	0.028	(-0.031, 0.087)	0.228	0.295	.349	112
	Model 2	Radiotherapy exposure	-0.346	(-0.833, 0.141)	0.228	0.295	.162	112
	Model 2	Body mass index	0.063	(0.014, 0.112)	0.228	0.295	.012	112
	Model 3	Intercept	-1.644	(-2.845, -0.443)	0.225	0.290	.008	112
	Model 3	Upper-body muscle strength	0.208	(0.115, 0.301)	0.225	0.290	.001	112
	Model 3	Time from treatment completion	0.026	(-0.032, 0.085)	0.225	0.290	.375	112
	Model 3	Radiotherapy exposure	-0.341	(-0.829, 0.147)	0.225	0.290	.169	112
	Model 3	Body mass index	0.060	(0.010, 0.109)	0.225	0.290	.019	112
	Model 3	Calcium intake	0.000	(-0.001, 0.000)	0.225	0.290	.457	112
	Model 4	Intercept	-3.324	(-4.921, -1.727)	0.273	0.376	.001	107
	Model 4	Upper-body muscle strength	0.156	(0.058, 0.253)	0.273	0.376	.002	107
	Model 4	Time from treatment completion	0.032	(-0.027, 0.091)	0.273	0.376	.290	107
	Model 4	Radiotherapy exposure	-0.179	(-0.693, 0.335)	0.273	0.376	.491	107
	Model 4	Body mass index	0.082	(0.031, 0.132)	0.273	0.376	.002	107
	Model 4	Calcium intake	0.000	(-0.001, 0.000)	0.273	0.376	.354	107
	Model 4	Total physical activity	0.005	(0.002, 0.008)	0.273	0.376	.002	107
Femoral neck aBMD Z-score	Model 0	Intercept	-0.846	(-1.250, -0.443)	0.114	0.129	.001	115
	Model 0	Upper-body muscle strength	0.209	(0.105, 0.314)	0.114	0.129	.001	115
	Model 1	Intercept	-0.849	(-1.396, -0.302)	0.183	0.224	.003	112
	Model 1	Upper-body muscle strength	0.194	(0.092, 0.297)	0.183	0.224	.000	112
	Model 1	Time from treatment completion	0.051	(-0.013, 0.116)	0.183	0.224	.116	112
	Model 1	Radiotherapy exposure	-0.732	(-1.275, -0.188)	0.183	0.224	.009	112
	Model 2	Intercept	-2.364	(-3.487, -1.240)	0.240	0.316	.001	112
	Model 2	Upper-body muscle strength	0.175	(0.076, 0.275)	0.240	0.316	.001	112
	Model 2	Time from treatment completion	0.034	(-0.029, 0.097)	0.240	0.316	.291	112
	Model 2	Radiotherapy exposure	-0.721	(-1.245, -0.197)	0.240	0.316	.007	112
	Model 2	Body mass index	0.080	(0.028, 0.133)	0.240	0.316	.003	112
	Model 3	Intercept	-2.340	(-3.636, -1.044)	0.233	0.304	.001	112

	Model 3	Upper-body muscle strength	0.175	(0.075, 0.275)	0.233	0.304	.001	112
	Model 3	Time from treatment completion	0.034	(-0.030, 0.097)	0.233	0.304	.296	112
	Model 3	Radiotherapy exposure	-0.720	(-1.247, -0.193)	0.233	0.304	.008	112
	Model 3	Body mass index	0.080	(0.026, 0.134)	0.233	0.304	.004	112
	Model 3	Calcium intake	0.000	(-0.001, 0.001)	0.233	0.304	.942	112
	Model 4	Intercept	-4.250	(-5.927, -2.573)	0.296	0.420	.001	107
	Model 4	Upper-body muscle strength	0.113	(0.011, 0.215)	0.296	0.420	.031	107
	Model 4	Time from treatment completion	0.037	(-0.025, 0.099)	0.296	0.420	.238	107
	Model 4	Radiotherapy exposure	-0.551	(-1.091, -0.012)	0.296	0.420	.045	107
	Model 4	Body mass index	0.106	(0.052, 0.159)	0.296	0.420	.001	107
	Model 4	Calcium intake	0.000	(-0.001, 0.000)	0.296	0.420	.831	107
	Model 4	Total physical activity	0.005	(0.002, 0.008)	0.296	0.420	.001	107
Lumbar spine aBMD Z-score	Model 0	Intercept	-0.713	(-1.098, -0.328)	0.123	0.140	.001	116
	Model 0	Upper-body muscle strength	0.209	(0.109, 0.310)	0.123	0.140	.001	116
	Model 1	Intercept	-0.680	(-1.228, -0.133)	0.113	0.128	.015	113
	Model 1	Upper-body muscle strength	0.210	(0.108, 0.312)	0.113	0.128	.001	113
	Model 1	Time from treatment completion	0.001	(-0.063, 0.064)	0.113	0.128	.984	113
	Model 1	Radiotherapy exposure	-0.123	(-0.667, 0.421)	0.113	0.128	.656	113
	Model 2	Intercept	-2.094	(-3.183, -1.006)	0.172	0.207	.001	113
	Model 2	Upper-body muscle strength	0.194	(0.095, 0.294)	0.172	0.207	.001	113
	Model 2	Time from treatment completion	-0.021	(-0.084, 0.042)	0.172	0.207	.512	113
	Model 2	Radiotherapy exposure	-0.104	(-0.631, 0.422)	0.172	0.207	.695	113
	Model 2	Body mass index	0.075	(0.025, 0.126)	0.172	0.207	.004	113
	Model 3	Intercept	-1.963	(-3.226, -0.700)	0.165	0.198	.003	113
	Model 3	Upper-body muscle strength	0.194	(0.094, 0.294)	0.165	0.198	.001	113
	Model 3	Time from treatment completion	-0.022	(-0.085, 0.042)	0.165	0.198	.499	113
	Model 3	Radiotherapy exposure	-0.102	(-0.630, 0.427)	0.165	0.198	.703	113
	Model 3	Body mass index	0.073	(0.022, 0.125)	0.165	0.198	.006	113
	Model 3	Calcium intake	0.000	(-0.001, 0.000)	0.165	0.198	.682	113
	Model 4	Intercept	-2.867	(-4.506, -1.229)	0.176	0.214	.001	108
	Model 4	Upper-body muscle strength	0.164	(0.058, 0.270)	0.176	0.214	.003	108
	Model 4	Time from treatment completion	-0.023	(-0.087, 0.042)	0.176	0.214	.490	108
	Model 4	Radiotherapy exposure	-0.051	(-0.618, 0.516)	0.176	0.214	.859	108
	Model 4	Body mass index	0.084	(0.031, 0.137)	0.176	0.214	.002	108
	Model 4	Calcium intake	0.000	(-0.001, 0.000)	0.176	0.214	.723	108
	Model 4	Total physical activity	0.003	(0.000, 0.006)	0.176	0.214	.098	108

Multiple linear regression analyses with several models of adjustment were performed as follows: model 0 (no adjustments), model 1 (adjusted for time from treatment completion to baseline evaluation [years] and radiotherapy exposure [yes/no]), model 2 (adjusted for covariates in model 1 plus body mass index [kg/m^2]), model 3 (adjusted for covariates in model 2 plus calcium intake [mg]) and model 4 (adjusted for covariates in model 3 plus total physical activity [min/day]). The criteria of f^2 statistic for small, medium, and large effect are 0.02, 0.15, and 0.35, respectively [(2)].

Table S5. Multiple lineal regressions for the associations of lower-body muscle strength with age-, sex- and race-specific areal bone mineral density (aBMD) Z-score at each site in young paediatric cancer survivors.

			B	95% CI	Adj. R^2	f^2	*P*	N
Total body (less head) aBMD Z-score	Model 0	Intercept	-0.522	(-0.937, -0.108)	0.028	0.028	.014	115
	Model 0	Lower-body muscle strength	0.126	(0.005, 0.247)	0.028	0.028	.042	115
	Model 1	Intercept	-0.226	(-0.801, 0.350)	0.096	0.106	.439	112
	Model 1	Lower-body muscle strength	0.089	(-0.031, 0.210)	0.096	0.106	.145	112
	Model 1	Time from treatment completion	0.007	(-0.059, 0.073)	0.096	0.106	.839	112
	Model 1	Radiotherapy exposure	-0.916	(-1.490, -0.342)	0.096	0.106	.002	112
	Model 2	Intercept	-3.050	(-4.287, -1.813)	0.260	0.351	.001	112
	Model 2	Lower-body muscle strength	0.183	(0.068, 0.298)	0.260	0.351	.002	112
	Model 2	Time from treatment completion	-0.032	(-0.094, 0.030)	0.260	0.351	.309	112
	Model 2	Radiotherapy exposure	-0.784	(-1.306, -0.261)	0.260	0.351	.004	112
	Model 2	Body mass index	0.131	(0.079, 0.183)	0.260	0.351	.001	112
	Model 3	Intercept	-3.174	(-4.594, -1.754)	0.254	0.340	.001	112
	Model 3	Lower-body muscle strength	0.185	(0.069, 0.302)	0.254	0.340	.002	112
	Model 3	Time from treatment completion	-0.031	(-0.093, 0.031)	0.254	0.340	.321	112
	Model 3	Radiotherapy exposure	-0.784	(-1.309, -0.260)	0.254	0.340	.004	112
	Model 3	Body mass index	0.133	(0.080, 0.187)	0.254	0.340	.001	112
	Model 3	Calcium intake	0.000	(0.000, 0.001)	0.254	0.340	.722	112
	Model 4	Intercept	-4.907	(-6.537, -3.277)	0.341	0.518	.001	107
	Model 4	Lower-body muscle strength	0.155	(0.039, 0.271)	0.341	0.518	.009	107
	Model 4	Time from treatment completion	-0.023	(-0.084, 0.037)	0.341	0.518	.443	107
	Model 4	Radiotherapy exposure	-0.575	(-1.108, -0.041)	0.341	0.518	.035	107
	Model 4	Body mass index	0.142	(0.091, 0.194)	0.341	0.518	.001	107
	Model 4	Calcium intake	0.000	(0.000, 0.001)	0.341	0.518	.939	107
	Model 4	Total physical activity	0.005	(0.003, 0.008)	0.341	0.518	.001	107
Total hip aBMD Z-score	Model 0	Intercept	-0.158	(-0.548, 0.232)	0.025	0.026	.424	114
	Model 0	Lower-body muscle strength	0.114	(0.000, 0.227)	0.025	0.026	.050	114
	Model 1	Intercept	-0.234	(-0.782, 0.313)	0.051	0.054	.398	111
	Model 1	Lower-body muscle strength	0.095	(-0.020, 0.210)	0.051	0.054	.106	111
	Model 1	Time from treatment completion	0.046	(-0.018, 0.110)	0.051	0.054	.156	111
	Model 1	Radiotherapy exposure	-0.410	(-0.956, 0.137)	0.051	0.054	.140	111
	Model 2	Intercept	-2.337	(-3.606, -1.067)	0.146	0.171	.001	111
	Model 2	Lower-body muscle strength	0.160	(0.045, 0.275)	0.146	0.171	.007	111
	Model 2	Time from treatment completion	0.023	(-0.039, 0.085)	0.146	0.171	.462	111
	Model 2	Radiotherapy exposure	-0.323	(-0.844, 0.198)	0.146	0.171	.221	111
	Model 2	Body mass index	0.098	(0.044, 0.151)	0.146	0.171	.001	111
	Model 3	Intercept	-2.189	(-3.639, -0.739)	0.140	0.162	.003	111
	Model 3	Lower-body muscle strength	0.157	(0.041, 0.273)	0.140	0.162	.009	111
	Model 3	Time from treatment completion	0.022	(-0.040, 0.085)	0.140	0.162	.479	111
	Model 3	Radiotherapy exposure	-0.322	(-0.845, 0.200)	0.140	0.162	.224	111
	Model 3	Body mass index	0.095	(0.040, 0.150)	0.140	0.162	.001	111
	Model 3	Calcium intake	0.000	(-0.001, 0.000)	0.140	0.162	.673	111
	Model 4	Intercept	-4.203	(-5.910, -2.496)	0.251	0.335	.001	106
	Model 4	Lower-body muscle strength	0.107	(-0.008, 0.221)	0.251	0.335	.067	106
	Model 4	Time from treatment completion	0.033	(-0.028, 0.093)	0.251	0.335	.286	106
	Model 4	Radiotherapy exposure	-0.096	(-0.623, 0.431)	0.251	0.335	.720	106
	Model 4	Body mass index	0.109	(0.056, 0.163)	0.251	0.335	.001	106
	Model 4	Calcium intake	0.000	(-0.001, 0.000)	0.251	0.335	.452	106
	Model 4	Total physical activity	0.006	(0.003, 0.009)	0.251	0.335	.001	106
Femoral neck aBMD Z-score	Model 0	Intercept	-0.446	(-0.871, -0.021)	0.011	0.011	.040	114
	Model 0	Lower-body muscle strength	0.094	(-0.030, 0.218)	0.011	0.011	.135	114
	Model 1	Intercept	-0.399	(-0.981, 0.182)	0.092	0.101	.176	111
	Model 1	Lower-body muscle strength	0.061	(-0.062, 0.183)	0.092	0.101	.328	111
	Model 1	Time from treatment completion	0.057	(-0.011, 0.125)	0.092	0.101	.102	111
	Model 1	Radiotherapy exposure	-0.804	(-1.384, -0.223)	0.092	0.101	.007	111
	Model 2	Intercept	-2.737	(-4.076, -1.398)	0.193	0.239	.001	111
	Model 2	Lower-body muscle strength	0.133	(0.011, 0.254)	0.193	0.239	.032	111
	Model 2	Time from treatment completion	0.031	(-0.035, 0.096)	0.193	0.239	.352	111
	Model 2	Radiotherapy exposure	-0.707	(-1.257, -0.158)	0.193	0.239	.012	111
	Model 2	Body mass index	0.109	(0.052, 0.165)	0.193	0.239	.001	111
	Model 3	Intercept	-2.801	(-4.332, -1.270)	0.185	0.228	.001	111

	Model 3	Lower-body muscle strength	0.134	(0.011, 0.256)	0.185	0.228	.033	111
	Model 3	Time from treatment completion	0.031	(-0.035, 0.097)	0.185	0.228	.350	111
	Model 3	Radiotherapy exposure	-0.708	(-1.260, -0.156)	0.185	0.228	.012	111
	Model 3	Body mass index	0.110	(0.051, 0.168)	0.185	0.228	.001	111
	Model 3	Calcium intake	0.000	(-0.001, 0.001)	0.185	0.228	.862	111
	Model 4	Intercept	-4.925	(-6.685, -3.164)	0.300	0.429	.001	106
	Model 4	Lower-body muscle strength	0.070	(-0.048, 0.188)	0.300	0.429	.240	106
	Model 4	Time from treatment completion	0.041	(-0.022, 0.103)	0.300	0.429	.197	106
	Model 4	Radiotherapy exposure	-0.495	(-1.039, 0.048)	0.300	0.429	.074	106
	Model 4	Body mass index	0.125	(0.070, 0.180)	0.300	0.429	.001	106
	Model 4	Calcium intake	0.000	(-0.001, 0.000)	0.300	0.429	.931	106
	Model 4	Total physical activity	0.007	(0.004, 0.010)	0.300	0.429	.001	106
Lumbar spine aBMD Z-score	Model 0	Intercept	-0.276	(-0.680, 0.128)	0.008	0.008	.179	115
	Model 0	Lower-body muscle strength	0.083	(-0.036, 0.201)	0.008	0.008	.169	115
	Model 1	Intercept	-0.228	(-0.812, 0.355)	-0.004	-0.004	.440	112
	Model 1	Lower-body muscle strength	0.078	(-0.044, 0.200)	-0.004	-0.004	.207	112
	Model 1	Time from treatment completion	0.006	(-0.061, 0.073)	-0.004	-0.004	.868	112
	Model 1	Radiotherapy exposure	-0.190	(-0.772, 0.392)	-0.004	-0.004	.518	112
	Model 2	Intercept	-2.484	(-3.792, -1.177)	0.105	0.117	.001	112
	Model 2	Lower-body muscle strength	0.153	(0.031, 0.275)	0.105	0.117	.014	112
	Model 2	Time from treatment completion	-0.025	(-0.091, 0.040)	0.105	0.117	.445	112
	Model 2	Radiotherapy exposure	-0.084	(-0.636, 0.468)	0.105	0.117	.763	112
	Model 2	Body mass index	0.105	(0.050, 0.160)	0.105	0.117	.001	112
	Model 3	Intercept	-2.441	(-3.943, -0.940)	0.097	0.107	.002	112
	Model 3	Lower-body muscle strength	0.152	(0.029, 0.276)	0.097	0.107	.016	112
	Model 3	Time from treatment completion	-0.025	(-0.091, 0.040)	0.097	0.107	.444	112
	Model 3	Radiotherapy exposure	-0.084	(-0.639, 0.471)	0.097	0.107	.764	112
	Model 3	Body mass index	0.104	(0.048, 0.161)	0.097	0.107	.001	112
	Model 3	Calcium intake	0.000	(-0.001, 0.001)	0.097	0.107	.907	112
	Model 4	Intercept	-3.675	(-5.446, -1.904)	0.146	0.171	.001	107
	Model 4	Lower-body muscle strength	0.122	(-0.004, 0.248)	0.146	0.171	.057	107
	Model 4	Time from treatment completion	-0.024	(-0.090, 0.041)	0.146	0.171	.466	107
	Model 4	Radiotherapy exposure	0.038	(-0.541, 0.618)	0.146	0.171	.896	107
	Model 4	Body mass index	0.110	(0.054, 0.166)	0.146	0.171	.001	107
	Model 4	Calcium intake	0.000	(-0.001, 0.001)	0.146	0.171	.857	107
	Model 4	Total physical activity	0.004	(0.001, 0.007)	0.146	0.171	.011	107

Multiple linear regression analyses with several models of adjustment were performed as follows: model 0 (no adjustments), model 1 (adjusted for time from treatment completion to baseline evaluation [years] and radiotherapy exposure [yes/no]), model 2 (adjusted for covariates in model 1 plus body mass index [kg/m^2]), model 3 (adjusted for covariates in model 2 plus calcium intake [mg]) and model 4 (adjusted for covariates in model 3 plus total physical activity [min/day]). The criteria of f^2 statistic for small, medium, and large effect are 0.02, 0.15, and 0.35, respectively [(2)].

Table S6. Multiple lineal regressions for the associations of upper-body muscle strength with age-, sex- and race-specific bone mineral content (BMC) Z-score at each site in young paediatric cancer survivors.

			B	95% CI	Adj. R^2	f^2	*P*	N
Total body (less head) BMC Z-score	Model 0	Intercept	-1.346	(-1.691, -1.002)	0.244	0.323	.001	116
	Model 0	Upper-body muscle strength	0.280	(0.190, 0.369)	0.244	0.323	.001	116
	Model 1	Intercept	-1.248	(-1.718, -0.778)	0.295	0.418	.001	113
	Model 1	Upper-body muscle strength	0.277	(0.189, 0.365)	0.295	0.418	.001	113
	Model 1	Time from treatment completion	0.008	(-0.046, 0.063)	0.295	0.418	.767	113
	Model 1	Radiotherapy exposure	-0.600	(-1.067, -0.132)	0.295	0.418	.012	113
	Model 2	Intercept	-2.967	(-3.864, -2.071)	0.395	0.653	.001	113
	Model 2	Upper-body muscle strength	0.258	(0.176, 0.340)	0.395	0.653	.001	113
	Model 2	Time from treatment completion	-0.018	(-0.070, 0.034)	0.395	0.653	.493	113
	Model 2	Radiotherapy exposure	-0.578	(-1.011, -0.145)	0.395	0.653	.009	113
	Model 2	Body mass index	0.092	(0.050, 0.133)	0.395	0.653	.001	113
	Model 3	Intercept	-3.004	(0.525, -4.044)	-1.964	-0.663	.001	113
	Model 3	Upper-body muscle strength	0.259	(0.042, 0.176)	0.341	0.517	.001	113
	Model 3	Time from treatment completion	-0.018	(0.026, -0.070)	0.034	0.035	.500	113
	Model 3	Radiotherapy exposure	-0.578	(0.220, -1.014)	-0.143	-0.125	.010	113
	Model 3	Body mass index	0.092	(0.021, 0.050)	0.135	0.156	.001	113
	Model 3	Calcium intake	0.000	(0.000, 0.000)	0.000	0.000	.890	113
	Model 4	Intercept	-4.612	(-5.901, -3.324)	0.461	0.855	.001	108
	Model 4	Upper-body muscle strength	0.222	(0.138, 0.306)	0.461	0.855	.001	108
	Model 4	Time from treatment completion	-0.010	(-0.060, 0.041)	0.461	0.855	.709	108
	Model 4	Radiotherapy exposure	-0.401	(-0.847, 0.045)	0.461	0.855	.077	108
	Model 4	Body mass index	0.108	(0.067, 0.150)	0.461	0.855	.001	108
	Model 4	Calcium intake	0.000	(0.000, 0.000)	0.461	0.855	.884	108
	Model 4	Total physical activity	0.004	(0.002, 0.007)	0.461	0.855	.001	108
Total hip BMC Z-score	Model 0	Intercept	-0.396	(-0.792, 0.000)	0.173	0.209	.050	115
	Model 0	Upper-body muscle strength	0.258	(0.156, 0.361)	0.173	0.209	.001	115
	Model 1	Intercept	-0.318	(-0.860, 0.225)	0.195	0.242	.248	112
	Model 1	Upper-body muscle strength	0.268	(0.166, 0.370)	0.195	0.242	.001	112
	Model 1	Time from treatment completion	-0.016	(-0.080, 0.048)	0.195	0.242	.620	112
	Model 1	Radiotherapy exposure	-0.284	(-0.824, 0.255)	0.195	0.242	.299	112
	Model 2	Intercept	-0.900	(-2.055, 0.255)	0.197	0.245	.125	112
	Model 2	Upper-body muscle strength	0.261	(0.158, 0.363)	0.197	0.245	.001	112
	Model 2	Time from treatment completion	-0.023	(-0.088, 0.042)	0.197	0.245	.488	112
	Model 2	Radiotherapy exposure	-0.280	(-0.819, 0.259)	0.197	0.245	.306	112
	Model 2	Body mass index	0.031	(-0.023, 0.085)	0.197	0.245	.260	112
	Model 3	Intercept	-0.890	(-2.222, 0.442)	0.190	0.235	.188	112
	Model 3	Upper-body muscle strength	0.261	(0.158, 0.364)	0.190	0.235	.001	112
	Model 3	Time from treatment completion	-0.023	(-0.088, 0.043)	0.190	0.235	.489	112
	Model 3	Radiotherapy exposure	-0.280	(-0.821, 0.262)	0.190	0.235	.308	112
	Model 3	Body mass index	0.031	(-0.024, 0.086)	0.190	0.235	.272	112
	Model 3	Calcium intake	0.000	(-0.001, 0.001)	0.190	0.235	.976	112
	Model 4	Intercept	-2.872	(-4.622, -1.122)	0.267	0.364	.002	107
	Model 4	Upper-body muscle strength	0.221	(0.114, 0.328)	0.267	0.364	.001	107
	Model 4	Time from treatment completion	-0.006	(-0.071, 0.059)	0.267	0.364	.857	107
	Model 4	Radiotherapy exposure	-0.103	(-0.666, 0.460)	0.267	0.364	.718	107
	Model 4	Body mass index	0.056	(0.000, 0.112)	0.267	0.364	.048	107
	Model 4	Calcium intake	0.000	(-0.001, 0.000)	0.267	0.364	.808	107
	Model 4	Total physical activity	0.005	(0.002, 0.008)	0.267	0.364	.003	107
Femoral neck BMC Z-score	Model 0	Intercept	-2.034	(-2.465, -1.604)	0.139	0.161	.001	115
	Model 0	Upper-body muscle strength	0.249	(0.137, 0.361)	0.139	0.161	.001	115
	Model 1	Intercept	-2.097	(-2.699, -1.494)	0.161	0.192	.001	112
	Model 1	Upper-body muscle strength	0.244	(0.131, 0.356)	0.161	0.192	.001	112
	Model 1	Time from treatment completion	0.037	(-0.034, 0.108)	0.161	0.192	.304	112
	Model 1	Radiotherapy exposure	-0.479	(-1.078, 0.120)	0.161	0.192	.116	112
	Model 2	Intercept	-4.180	(-5.388, -2.971)	0.258	0.348	.001	112
	Model 2	Upper-body muscle strength	0.218	(0.111, 0.325)	0.258	0.348	.001	112
	Model 2	Time from treatment completion	0.013	(-0.055, 0.081)	0.258	0.348	.712	112
	Model 2	Radiotherapy exposure	-0.464	(-1.028, 0.100)	0.258	0.348	.106	112
	Model 2	Body mass index	0.110	(0.054, 0.167)	0.258	0.348	.001	112
	Model 3	Intercept	-4.766	(-6.140, -3.391)	0.271	0.372	.001	112

	Model 3	Upper-body muscle strength	0.219	(0.113, 0.325)	0.271	0.372	.001	112
	Model 3	Time from treatment completion	0.016	(-0.051, 0.084)	0.271	0.372	.634	112
	Model 3	Radiotherapy exposure	-0.477	(-1.036, 0.082)	0.271	0.372	.094	112
	Model 3	Body mass index	0.119	(0.062, 0.176)	0.271	0.372	.001	112
	Model 3	Calcium intake	0.000	(0.000, 0.001)	0.271	0.372	.088	112
	Model 4	Intercept	-6.057	(-7.923, -4.191)	0.292	0.412	.001	107
	Model 4	Upper-body muscle strength	0.190	(0.076, 0.304)	0.292	0.412	.001	107
	Model 4	Time from treatment completion	0.024	(-0.045, 0.094)	0.292	0.412	.484	107
	Model 4	Radiotherapy exposure	-0.438	(-1.039, 0.162)	0.292	0.412	.151	107
	Model 4	Body mass index	0.138	(0.079, 0.198)	0.292	0.412	.001	107
	Model 4	Calcium intake	0.001	(0.000, 0.001)	0.292	0.412	.081	107
	Model 4	Total physical activity	0.003	(0.000, 0.006)	0.292	0.412	.077	107
	Model 0	Intercept	-1.122	(-1.482, -0.762)	0.152	0.179	.001	116
	Model 0	Upper-body muscle strength	0.220	(0.126, 0.313)	0.152	0.179	.001	116
	Model 1	Intercept	-1.105	(-1.609, -0.602)	0.167	0.200	.001	113
	Model 1	Upper-body muscle strength	0.220	(0.126, 0.314)	0.167	0.200	.001	113
	Model 1	Time from treatment completion	0.012	(-0.046, 0.070)	0.167	0.200	.682	113
	Model 1	Radiotherapy exposure	-0.353	(-0.854, 0.148)	0.167	0.200	.165	113
	Model 2	Intercept	-2.340	(-3.346, -1.333)	0.215	0.275	.001	113
	Model 2	Upper-body muscle strength	0.207	(0.115, 0.299)	0.215	0.275	.001	113
	Model 2	Time from treatment completion	-0.007	(-0.065, 0.052)	0.215	0.275	.821	113
	Model 2	Radiotherapy exposure	-0.337	(-0.824, 0.149)	0.215	0.275	.172	113
	Model 2	Body mass index	0.066	(0.019, 0.113)	0.215	0.275	.006	113
Lumbar spine BMC Z-score	Model 3	Intercept	-2.608	(-3.772, -1.445)	0.214	0.273	.001	113
	Model 3	Upper-body muscle strength	0.207	(0.115, 0.300)	0.214	0.273	.001	113
	Model 3	Time from treatment completion	-0.005	(-0.063, 0.053)	0.214	0.273	.863	113
	Model 3	Radiotherapy exposure	-0.343	(-0.830, 0.144)	0.214	0.273	.165	113
	Model 3	Body mass index	0.070	(0.022, 0.117)	0.214	0.273	.005	113
	Model 3	Calcium intake	0.000	(0.000, 0.001)	0.214	0.273	.363	113
	Model 4	Intercept	-3.155	(-4.673, -1.636)	0.219	0.280	.001	108
	Model 4	Upper-body muscle strength	0.201	(0.103, 0.300)	0.219	0.280	.001	108
	Model 4	Time from treatment completion	0.001	(-0.059, 0.061)	0.219	0.280	.981	108
	Model 4	Radiotherapy exposure	-0.322	(-0.848, 0.203)	0.219	0.280	.226	108
	Model 4	Body mass index	0.076	(0.027, 0.125)	0.219	0.280	.003	108
	Model 4	Calcium intake	0.000	(0.000, 0.001)	0.219	0.280	.333	108
	Model 4	Total physical activity	0.001	(-0.002, 0.004)	0.219	0.280	.384	108

Multiple linear regression analyses with several models of adjustment were performed as follows: model 0 (no adjustments), model 1 (adjusted for time from treatment completion to baseline evaluation [years] and radiotherapy exposure [yes/no]), model 2 (adjusted for covariates in model 1 plus body mass index [kg/m^2]), model 3 (adjusted for covariates in model 2 plus calcium intake [mg]) and model 4 (adjusted for covariates in model 3 plus total physical activity [min/day]). The criteria of f^2 statistic for small, medium, and large effect are 0.02, 0.15, and 0.35, respectively [(2)].

Table S7. Multiple lineal regressions for the associations of lower-body muscle strength with age-, sex- and race-specific bone mineral content (BMC) Z-score at each site in young paediatric cancer survivors.

			B	95% CI	Adj. R^2	f^2	*P*	N
Total body (less head) BMC Z-score	Model 0	Intercept	-0.757	(-1.148, -0.366)	0.018	0.018	.001	115
	Model 0	Lower-body muscle strength	0.102	(-0.012, 0.216)	0.018	0.018	.080	115
	Model 1	Intercept	-0.558	(-1.108, -0.008)	0.058	0.062	.047	112
	Model 1	Lower-body muscle strength	0.070	(-0.045, 0.185)	0.058	0.062	.228	112
	Model 1	Time from treatment completion	0.011	(-0.052, 0.075)	0.058	0.062	.721	112
	Model 1	Radiotherapy exposure	-0.700	(-1.248, -0.152)	0.058	0.062	.013	112
	Model 2	Intercept	-3.305	(-4.480, -2.130)	0.236	0.309	.001	112
	Model 2	Lower-body muscle strength	0.161	(0.052, 0.271)	0.236	0.309	.004	112
	Model 2	Time from treatment completion	-0.026	(-0.085, 0.033)	0.236	0.309	.378	112
	Model 2	Radiotherapy exposure	-0.571	(-1.067, -0.075)	0.236	0.309	.025	112
	Model 2	Body mass index	0.128	(0.078, 0.177)	0.236	0.309	.001	112
	Model 3	Intercept	-3.429	(-4.778, -2.080)	0.230	0.299	.001	112
	Model 3	Lower-body muscle strength	0.164	(0.053, 0.274)	0.230	0.299	.004	112
	Model 3	Time from treatment completion	-0.026	(-0.085, 0.033)	0.230	0.299	.392	112
	Model 3	Radiotherapy exposure	-0.571	(-1.070, -0.073)	0.230	0.299	.025	112
	Model 3	Body mass index	0.130	(0.079, 0.180)	0.230	0.299	.001	112
	Model 3	Calcium intake	0.000	(0.000, 0.001)	0.230	0.299	.709	112
	Model 4	Intercept	-5.427	(-6.925, -3.928)	0.365	0.575	.001	107
	Model 4	Lower-body muscle strength	0.130	(0.023, 0.236)	0.365	0.575	.017	107
	Model 4	Time from treatment completion	-0.015	(-0.071, 0.040)	0.365	0.575	.587	107
	Model 4	Radiotherapy exposure	-0.305	(-0.795, 0.186)	0.365	0.575	.220	107
	Model 4	Body mass index	0.140	(0.092, 0.187)	0.365	0.575	.001	107
	Model 4	Calcium intake	0.000	(0.000, 0.000)	0.365	0.575	.987	107
	Model 4	Total physical activity	0.006	(0.004, 0.009)	0.365	0.575	.001	107
Total hip BMC Z-score	Model 0	Intercept	-0.056	(-0.479, 0.368)	0.054	0.057	.795	114
	Model 0	Lower-body muscle strength	0.169	(0.046, 0.292)	0.054	0.057	.008	114
	Model 1	Intercept	0.096	(-0.503, 0.695)	0.044	0.046	.751	111
	Model 1	Lower-body muscle strength	0.154	(0.028, 0.280)	0.044	0.046	.017	111
	Model 1	Time from treatment completion	-0.013	(-0.083, 0.057)	0.044	0.046	.707	111
	Model 1	Radiotherapy exposure	-0.303	(-0.901, 0.294)	0.044	0.046	.316	111
	Model 2	Intercept	-1.553	(-2.981, -0.125)	0.089	0.098	.033	111
	Model 2	Lower-body muscle strength	0.205	(0.075, 0.334)	0.089	0.098	.002	111
	Model 2	Time from treatment completion	-0.031	(-0.101, 0.038)	0.089	0.098	.374	111
	Model 2	Radiotherapy exposure	-0.236	(-0.821, 0.350)	0.089	0.098	.427	111
	Model 2	Body mass index	0.077	(0.016, 0.137)	0.089	0.098	.014	111
	Model 3	Intercept	-1.655	(-3.287, -0.023)	0.081	0.088	.047	111
	Model 3	Lower-body muscle strength	0.207	(0.076, 0.337)	0.081	0.088	.002	111
	Model 3	Time from treatment completion	-0.031	(-0.101, 0.039)	0.081	0.088	.385	111
	Model 3	Radiotherapy exposure	-0.236	(-0.825, 0.352)	0.081	0.088	.428	111
	Model 3	Body mass index	0.078	(0.016, 0.140)	0.081	0.088	.014	111
	Model 3	Calcium intake	0.000	(-0.001, 0.001)	0.081	0.088	.795	111
	Model 4	Intercept	-4.119	(-6.031, -2.207)	0.218	0.279	.001	106
	Model 4	Lower-body muscle strength	0.177	(0.049, 0.305)	0.218	0.279	.007	106
	Model 4	Time from treatment completion	-0.010	(-0.078, 0.058)	0.218	0.279	.770	106
	Model 4	Radiotherapy exposure	0.033	(-0.557, 0.623)	0.218	0.279	.912	106
	Model 4	Body mass index	0.100	(0.040, 0.160)	0.218	0.279	.001	106
	Model 4	Calcium intake	0.000	(-0.001, 0.001)	0.218	0.279	.972	106
	Model 4	Total physical activity	0.007	(0.003, 0.010)	0.218	0.279	.001	106
Femoral neck BMC Z-score	Model 0	Intercept	-1.537	(-2.000, -1.074)	0.010	0.010	.001	114
	Model 0	Lower-body muscle strength	0.099	(-0.036, 0.233)	0.010	0.010	.150	114
	Model 1	Intercept	-1.522	(-2.179, -0.864)	0.029	0.030	.001	111
	Model 1	Lower-body muscle strength	0.071	(-0.067, 0.209)	0.029	0.030	.312	111
	Model 1	Time from treatment completion	0.039	(-0.038, 0.116)	0.029	0.030	.316	111
	Model 1	Radiotherapy exposure	-0.552	(-1.208, 0.104)	0.029	0.030	.098	111
	Model 2	Intercept	-4.749	(-6.213, -3.285)	0.194	0.241	.001	111
	Model 2	Lower-body muscle strength	0.170	(0.038, 0.303)	0.194	0.241	.012	111
	Model 2	Time from treatment completion	0.004	(-0.068, 0.075)	0.194	0.241	.921	111
	Model 2	Radiotherapy exposure	-0.419	(-1.020, 0.181)	0.194	0.241	.169	111
	Model 2	Body mass index	0.150	(0.088, 0.212)	0.194	0.241	.001	111
	Model 3	Intercept	-5.488	(-7.135, -3.842)	0.212	0.269	.001	111

	Model 3	Lower-body muscle strength	0.184	(0.052, 0.316)	0.212	0.269	.007	111
	Model 3	Time from treatment completion	0.007	(-0.064, 0.078)	0.212	0.269	.837	111
	Model 3	Radiotherapy exposure	-0.423	(-1.017, 0.170)	0.212	0.269	.160	111
	Model 3	Body mass index	0.162	(0.099, 0.224)	0.212	0.269	.001	111
	Model 3	Calcium intake	0.001	(0.000, 0.001)	0.212	0.269	.065	111
	Model 4	Intercept	-7.106	(-9.129, -5.083)	0.258	0.348	.001	106
	Model 4	Lower-body muscle strength	0.162	(0.026, 0.297)	0.258	0.348	.020	106
	Model 4	Time from treatment completion	0.018	(-0.054, 0.090)	0.258	0.348	.618	106
	Model 4	Radiotherapy exposure	-0.315	(-0.940, 0.309)	0.258	0.348	.319	106
	Model 4	Body mass index	0.178	(0.114, 0.241)	0.258	0.348	.001	106
	Model 4	Calcium intake	0.001	(0.000, 0.001)	0.258	0.348	.067	106
	Model 4	Total physical activity	0.004	(0.001, 0.008)	0.258	0.348	.015	106
	Model 0	Intercept	-0.672	(-1.058, -0.285)	0.011	0.011	.001	115
	Model 0	Lower-body muscle strength	0.086	(-0.027, 0.199)	0.011	0.011	.134	115
	Model 1	Intercept	-0.586	(-1.139, -0.033)	0.017	0.017	.038	112
	Model 1	Lower-body muscle strength	0.066	(-0.050, 0.181)	0.017	0.017	.264	112
	Model 1	Time from treatment completion	0.015	(-0.048, 0.079)	0.017	0.017	.633	112
	Model 1	Radiotherapy exposure	-0.428	(-0.979, 0.124)	0.017	0.017	.127	112
	Model 2	Intercept	-2.620	(-3.867, -1.372)	0.113	0.128	.001	112
	Model 2	Lower-body muscle strength	0.133	(0.017, 0.249)	0.113	0.128	.025	112
	Model 2	Time from treatment completion	-0.012	(-0.075, 0.050)	0.113	0.128	.693	112
	Model 2	Radiotherapy exposure	-0.332	(-0.859, 0.194)	0.113	0.128	.214	112
	Model 2	Body mass index	0.094	(0.042, 0.147)	0.113	0.128	.001	112
Lumbar spine BMC Z-score	Model 3	Intercept	-2.996	(-4.421, -1.571)	0.115	0.130	.001	112
	Model 3	Lower-body muscle strength	0.140	(0.023, 0.257)	0.115	0.130	.019	112
	Model 3	Time from treatment completion	-0.011	(-0.073, 0.052)	0.115	0.130	.736	112
	Model 3	Radiotherapy exposure	-0.334	(-0.860, 0.192)	0.115	0.130	.211	112
	Model 3	Body mass index	0.100	(0.047, 0.154)	0.115	0.130	.001	112
	Model 3	Calcium intake	0.000	(0.000, 0.001)	0.115	0.130	.282	112
	Model 4	Intercept	-4.009	(-5.709, -2.309)	0.146	0.171	.001	107
	Model 4	Lower-body muscle strength	0.142	(0.022, 0.263)	0.146	0.171	.021	107
	Model 4	Time from treatment completion	-0.005	(-0.068, 0.058)	0.146	0.171	.864	107
	Model 4	Radiotherapy exposure	-0.218	(-0.774, 0.339)	0.146	0.171	.439	107
	Model 4	Body mass index	0.108	(0.054, 0.162)	0.146	0.171	.001	107
	Model 4	Calcium intake	0.000	(0.000, 0.001)	0.146	0.171	.288	107
	Model 4	Total physical activity	0.003	(0.000, 0.006)	0.146	0.171	.075	107

Multiple linear regression analyses with several models of adjustment were performed as follows: model 0 (no adjustments), model 1 (adjusted for time from treatment completion to baseline evaluation [years] and radiotherapy exposure [yes/no]), model 2 (adjusted for covariates in model 1 plus body mass index [kg/m^2]), model 3 (adjusted for covariates in model 2 plus calcium intake [mg]) and model 4 (adjusted for covariates in model 3 plus total physical activity [min/day]). The criteria of f^2 statistic for small, medium, and large effect are 0.02, 0.15, and 0.35, respectively [(2)].

Table S8. Odds ratios of low age-, sex- and race-specific areal bone mineral density (aBMD) and bone mineral content (BMC) Z-score at each site per one standard deviation score lower in upper-body and lower-body muscle strength (Reference deciles using FitBack reference values).

		Upper-body muscle strength		Lower-body muscle strength	
		OR	95% CI	OR	95% CI
Total body (less head) aBMD Z-score	Model 0	1.98	(1.41, 3.16)	1.29	(1.01, 1.72)
	Model 1	1.93	(1.38, 3.02)	1.18	(0.94, 1.56)
	Model 2	1.95	(1.38, 3.11)	1.36	(1.05, 1.87)
	Model 3	1.96	(1.38, 3.11)	1.37	(1.05, 1.89)
	Model 4	2.00	(1.35, 3.39)	1.40	(1.03, 2.06)
Total hip aBMD Z-score	Model 0	1.41	(1.07, 2.05)	1.69	(1.16, 2.82)
	Model 1	1.38	(1.05, 1.96)	1.55	(1.08, 2.56)
	Model 2	1.36	(1.04, 1.95)	1.70	(1.15, 2.92)
	Model 3	1.37	(1.04, 1.96)	1.68	(1.14, 2.89)
	Model 4	1.31	(0.98, 1.91)	1.56	(1.04, 2.71)
Femoral neck aBMD Z-score	Model 0	1.34	(1.07, 1.76)	1.29	(1.01, 1.73)
	Model 1	1.32	(1.05, 1.76)	1.26	(0.98, 1.73)
	Model 2	1.31	(1.04, 1.74)	1.35	(1.03, 1.89)
	Model 3	1.32	(1.04, 1.75)	1.34	(1.02, 1.88)
	Model 4	1.24	(0.96, 1.69)	1.23	(0.92, 1.76)
Lumbar spine aBMD Z-score	Model 0	1.32	(1.05, 1.75)	1.15	(0.92, 1.50)
	Model 1	1.31	(1.04, 1.76)	1.15	(0.91, 1.53)
	Model 2	1.30	(1.03, 1.73)	1.24	(0.96, 1.70)
	Model 3	1.31	(1.03, 1.76)	1.22	(0.94, 1.66)
	Model 4	1.28	(0.99, 1.74)	1.14	(0.87, 1.58)
Total bod (less head) BMC Z-score	Model 0	1.69	(1.30, 2.35)	1.13	(0.93, 1.41)
	Model 1	1.66	(1.28, 2.30)	1.07	(0.87, 1.33)
	Model 2	1.65	(1.27, 2.29)	1.16	(0.94, 1.48)
	Model 3	1.66	(1.27, 2.32)	1.18	(0.95, 1.50)
	Model 4	1.58	(1.18, 2.27)	1.11	(0.86, 1.48)
Total hip BMC Z-score	Model 0	1.46	(1.10, 2.12)	1.65	(1.16, 2.64)
	Model 1	1.45	(1.10, 2.10)	1.63	(1.14, 2.64)
	Model 2	1.46	(1.10, 2.13)	1.73	(1.18, 2.88)
	Model 3	1.46	(1.10, 2.13)	1.72	(1.18, 2.88)
	Model 4	1.37	(1.00, 2.07)	1.72	(1.14, 2.94)
Femoral neck BMC Z-score	Model 0	1.37	(1.15, 1.66)	1.19	(1.00, 1.44)
	Model 1	1.39	(1.16, 1.70)	1.15	(0.96, 1.40)
	Model 2	1.42	(1.17, 1.76)	1.39	(1.12, 1.77)
	Model 3	1.42	(1.17, 1.77)	1.42	(1.14, 1.82)
	Model 4	1.43	(1.16, 1.81)	1.40	(1.11, 1.80)
Lumbar spine BMC Z-score	Model 0	1.38	(1.11, 1.81)	1.08	(0.88, 1.35)
	Model 1	1.41	(1.12, 1.87)	1.06	(0.87, 1.33)
	Model 2	1.39	(1.11, 1.85)	1.17	(0.94, 1.51)
	Model 3	1.41	(1.12, 1.88)	1.19	(0.96, 1.54)
	Model 4	1.41	(1.09, 1.93)	1.23	(0.96, 1.65)

Binary logistic regression (low aBMD identified as Z-score less than -1.0, according to according to van Atteveld et al. [3] and normal aBMD identified as Z-score higher than -1.0) was used to estimate odds ratios with 95% confidence intervals. Same analyses were conducted for BMC Z-score. Adjusted models were as follows: model 0 (no adjustments), model 1 (adjusted for time from treatment completion to baseline evaluation [years] and radiotherapy exposure [yes/no]), model 2 (adjusted for covariates in model 1 plus body mass index [kg/m^2]), model 3 (adjusted for covariates in model 2 plus calcium intake [mg]) and model 4 (adjusted for covariates in model 3 plus total physical activity [min/day]). Age-, sex- and race-specific aBMD and BMC Z-score at each site are presented using international reference data from the Bone Mineral Density in Childhood Study [1].

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Chapter 9. Comorbid sarcopenia and low bone mineral density in young pediatric cancer survivors

Abstract

Background. Sarcopenia and low aBMD are prevalent musculoskeletal complications after pediatric cancer treatment. However, their relationship has not been examined in young pediatric cancers survivors. This study aimed to evaluate aBMD differences according to sarcopenia status and the risk of low aBMD Z-score in young pediatric cancer survivors with sarcopenia confirmed/probable.

Methods. This cross-sectional study included 116 pediatric cancer survivors (12.1 ± 3.3 years old; 42.2% female). Handgrip strength was used to assessed muscle strength. DXA estimated aBMD (g/cm^2) and appendicular lean mass index (ALMI, kg/m^2). "No sarcopenia" was defined when muscle strength was > decile 2. "Sarcopenia probable" was defined when muscle strength was < decile 2 and ALMI Z-score was > -1.5 SD. "Sarcopenia confirmed" was defined when muscle strength was < decile 2 and ALMI Z-score < -1.5 SD. Analysis of covariance and logistic regression, adjusted for time from treatment completion, radiotherapy exposure, calcium intake and physical activity, were used to evaluate aBMD and estimate the ORs of low aBMD (aBMD Z-score < -1.0).

Results. Survivors with sarcopenia confirmed had significantly lower aBMD than those without sarcopenia at total body (-1.2 [95% CI: -1.5 to -0.8] vs. 0.2 [-0.2 to 0.6], P < .001), lumbar spine (-0.7 [-1.1 to -0.3] vs. 0.4 [0.0 to 0.8], P < .001), total hip (-0.5 [-0.9 to -0.2] vs. 0.4 [0.1 to 0.8], P < .001) and femoral neck (-1.0 [-1.4 to -0.6] vs. 0.1 [-0.3 to 0.4], P = .001). Compared to survivors with sarcopenia probable, survivors with sarcopenia confirmed had significantly lower aBMD Z-score at total body (-1.2 [-1.5 to -0.8] vs. -0.2 [-0.7 to 0.4], P = .009), total hip (-0.5 [-0.9 to -0.2] vs. 0.5 [-0.1 to 1.0], P = .010) and femoral neck (-1.0 [-1.4 to -0.6] vs. 0.1 [-0.5 to 0.7], P = .014). Survivors with sarcopenia confirmed were at higher risk of low aBMD Z-score at the total body (OR: 6.91, 95% CI: 2.31-24.15), total hip (OR: 2.98, 1.02-9.54) and femoral neck (OR: 4.72, 1.72-14.19), than those without sarcopenia. Survivors with sarcopenia probable were at higher risk of low aBMD Z-score at the total body (OR: 4.13, 1.04-17.60), than those without sarcopenia.

Conclusions. Young pediatric cancer survivors with sarcopenia present higher risk of low aBMD. Resistance training-based interventions designed to mitigate osteosarcopenia in this population should be implemented at early stages.

Introduction

Pediatric cancer survival has significantly increased over the past 60 years reaching current 5-year survival rates of 85% in children and 82% in adolescents [1]. However, required treatments to cure cancer at such a young age increase the risk of later health-related complications (2). Low aBMD, defined by age-, sex- and race-specific aBMD Z-score less than -1.0 SD, has been reported in up to two-thirds of survivors [3]. Early exposure to DNA damaging agents during childhood, during a vital period of active skeletal growth, decreases bone formation and increases bone resorption affecting bone development [4,5]. Moreover, these treatments not only interfere with bone health, but also impact lean muscle mass and function [6]. Pediatric cancer survivors present these limitations (hereafter referred to as sarcopenia) [7] due to myofibrillary atrophy caused by degradation of myosin heavy chain and decrease in myosin synthesis death [8].

Sarcopenia is currently considered a public health burden not only during adulthood [9], but also during childhood [10]. It has been associated with a noteworthy vulnerability of adverse health outcomes following pediatric cancer treatment, including death [11]. A previous study identified that sarcopenic adults had a four-fold higher risk of having osteoporosis compared with non-sarcopenic individuals [12]. In adult pediatric cancer survivors, sarcopenia, pre-frailty and frailty (including low aBMD) have been reported to coexist at a mean age of 33 years [13]. However, the literature depicting the associations of sarcopenia and low aBMD in this population is still scarce. Whether sarcopenia is associated with low aBMD right after pediatric cancer treatment completion, its detection could help survivors to be screened for low aBMD. This is relevant since sarcopenia diagnosis could anticipate further decline in aBMD, which is more exacerbated than in healthy population [3].

The aims of this study were: i) to evaluate aBMD differences according to sarcopenia status; and ii) to examine the risk of low aBMD Z-score in young pediatric cancer survivors with sarcopenia confirmed/probable. We hypothesized that survivors with sarcopenia would significantly present lower aBMD Z-score and higher risk of low aBMD Z-score than those without sarcopenia.

Methods

Study Design and Participants

This cross-sectional study included 116 young pediatric cancer survivors (12.1±3.3 years old; 42% female) from the iBoneFIT project framework. A detailed description of the study protocol has been published elsewhere [14,15]. Briefly, iBoneFIT is a multicenter parallel group

randomized controlled trial designed to examine the effect of a 9-month online exercise program on bone health in young pediatric cancer survivors [14]. Survivors were recruited from the Units of Pediatric Oncology and Hematology of the 'Virgen de las Nieves' (Granada) and 'Reina Sofia' (Cordoba) University Hospitals. Inclusion criteria were one or more-year survivors aged 6 to 18 years, not currently receiving treatments for cancer, at previous exposure to radiotherapy and/or chemotherapy. All measurements were conducted during in two waves due to COVID-19 restrictions: first, from October to February 2020/2021; and second, from December to March 2021/2022. All parents and survivors provided written informed consent and assent before entering the trial, respectively. The iBoneFIT project was approved by the Ethics Committee on Human Research of Regional Government of Andalusia (Reference: 4500, December 2019), followed the ethical guidelines of the Declaration of Helsinki (revised version 2013), and the randomized controlled trial was registered (https://www.isrctn.com/ISRCTN61195625). This study was reported according to the STROBE checklist (**Table S1**). Although we recruited 116 young pediatric cancer survivors in total, sample size slightly varies for some variables due to missing data (i.e., some survivors were unable to perform some of the tests, were afraid of being scanned using DXA or declined a particular test during their assessment).

Anthropometry and Somatic Maturity

Body mass (kg) was evaluated with an electronic scale (SECA 861, Hamburg, Germany) with an accuracy of 100 g. Stature (cm) was assessed using a precision stadiometer (SECA 225, Hamburg, Germany) to the nearest 0.1 cm. Body mass index was calculated as body mass (kg)/stature (m^2). Additionally, age- and sex-specific body mass index Z-score and categories were calculated using international reference data for pediatric population [16]. Somatic maturity was measured using the prediction of years before or after peak height velocity using validated algorithms for boys and girls [17].

Clinical Data

Medical records were used to retrieve information regarding diagnosis, time from treatment completion to baseline data collection and treatment exposures (radiotherapy, chemotherapy and/or surgery, alone or in combination). Time from treatment completion (years) was treated as a continuous variable and treatment exposure as a dichotomous variable, radiotherapy (yes/no). Daily calcium (mg) intake was estimated by a validated specific food-frequency questionnaire [18].

Physical Activity

Tri-axial ActiGraph wGT3x-BT accelerometers (ActiGraph GT3X, Pensacola, FL, USA) were used to measure total physical activity (min/day) for seven consecutive days (24 hours/day). Survivors were instructed to wear devices on the non-dominant wrist except for water activities. Accelerometers were initialized at a sampling frequency of 90 Hz and raw data were processed using the GGIR R open-source package version 2.8-2. Euclidean Norm of the raw acceleration minus one G with negative values rounded to zero (ENMO) was calculated, as well as the angle of the z-axis of the device to estimate physical activity and sleep parameters [19]. Non-wear time was detected based on the standard deviation of the raw accelerations recorded in the three accelerometer axes as described elsewhere [20], and then imputed by means of the acceleration in the rest of the days at the same time window. Appropriate thresholds were used to identify physical activity intensities (i.e., Moderate-to-vigorous physical activity: 200 mg and light physical activity: 35-200 mg) [21]. We considered a day valid when: 1) the accelerometer registered at least 23 hours/day and 2) survivors wore the accelerometers on at least 16 hours/day since in this study the accelerometers were worn at both day and night [22]. Survivors having at least one valid day were included (sensibility analyses showed similar results when compared to including participants having at least three valid weekdays and one weekend day). Total physical activity was calculated as the sum of daily average moderate-to-vigorous physical activity and light physical activity (mean of all seven days).

Dual-energy X-ray Absorptiometry (DXA)

Survivors were evaluated using a single DXA scanner (Hologic Series Discovery QDR, Bedford, MA, USA) and analyzed by APEX software (version 4.0.2). The device was calibrated each day using a lumbar spine phantom. Survivors were asked to remain still and scanned in the supine position according to the ISCD [23]. Three regions were analyzed (total body, lumbar spine and right hip) to characterize aBMD (g/cm^2) and BMC (g) of total body (less head), lumbar spine (mean of L1–L4), total hip and femoral neck. A total body scan was used to obtain lean mass (kg) [body mass – (fat mass + bone mass)] of the arms and legs (appendicular lean mass), and of total body, and the trunk. ALMI, kg/m^2 was calculated by dividing appendicular lean mass by stature. A single trained researcher analyzed all DXA scans. DXA coefficient of variation in pediatric population ranges between 1.0 and 2.9%, depending on the region [24].

Using international reference data from the Bone Mineral Density in Childhood Study [25], age-, sex- and race-specific aBMD and BMC Z-score at total body, lumbar spine, total hip and femoral neck were calculated for all analyses. Survivors with aBMD or BMC Z-score < -1.0 SD were classified with low aBMD or BMC, respectively [3]. We used the same database to calculate age-, sex- and race-specific ALMI Z-score for analyses [26]. Survivors with ALMI < -1.5 SD were classified with low ALMI as previous studies have conducted [11].

Muscle Strength

Handgrip (upper-body muscle strength) was evaluated with a dynamometer (TKK 5101 Grip D, Takei, Tokyo, Japan). This is a valid (ICC, 0.73 - 0.91), and reproducible test (ICC, 0.91 - 0.93) [27]. Survivors, keeping the arm straight, squeezed the dynamometer during five seconds twice by each hand and the best scores in kilograms were averaged.

To get an appropriate insight into the status of muscle strength in our sample, performance on each test was compared with updated age- and sex-specific reference values of healthy young population based on nearly eight million test results from 34 countries gathered by the FitBack network [28]. Muscle strength deficits were identified as < decile 2 following previous sex-and age-specific percentiles definitions of fitness deficits first published by Blair et al. [29].

Sarcopenia

Sarcopenia status definition was followed according to the EWGSOP2 (**Figure 1**) [30], following previous reports in this population [13]. "No sarcopenia" was defined when muscle strength was > decile 2. "Sarcopenia probable" was defined when muscle strength was < decile 2 and ALMI Z-score was > -1.5 SD. "Sarcopenia confirmed" was defined when muscle strength was < decile 2 and ALMI Z-score < -1.5 SD. Given that the cut-off points of the EWGSOP2 were based on adults, we compared muscle strength and ALMI with international reference data of healthy young population, as previously mentioned.

Statistical Analysis

Variable distributions were checked and verified using skewness and kurtosis, Kolmogorov-Smirnov test, visual check of histograms, Q-Q and box plots. Descriptive data were reported as mean and SD or as frequencies (percentages).

Analysis of covariance was used to test to evaluate aBMD score (outcome variable) according to sarcopenia status. Covariates included the time from treatment completion, radiotherapy exposure, calcium intake and total physical activity. To identify the MSAS for the differences

in aBMD and BMC Z-score according sarcopenia status, we built a theoretical causal diagram based on previous associations with muscle strength, lean mass and/or aBMD and BMC available in the scientific literature [2,31,32]. We used the online tool DAGitty to construct a DAG [33]. The covariates age, sex, time from treatment completion, radiotherapy exposure, calcium intake and physical activity were identified as the MSAS (**Figure S1**). Binary logistic regression models were used to estimate the odds of low aBMD of survivors with sarcopenia confirmed/probable. The same analyses were repeated with BMC Z-score as the outcome. Results are presented as ORs with 95%CIs. Statistical analyses were performed using the statistical software R version 4.0.3 (R Foundation for Statistical Computing), B coefficient was presented non-standardized, and P-values < .05 were considered statistically significant.

Results

A total of 196 young pediatric cancer survivors were initially approached for participation. After inclusion/exclusion criteria screening, 116 were enrolled and included in this study (**Figure S2**).

Participant characteristics

Descriptive characteristics of the sample are presented in **Table 1**. Survivors were a mean (SD) age of 12.1 (3.3) years, 42.2% were female and the majority was diagnosed with blood cancers (60.9%). **Table 2** shows that more than one-third of survivors presented sarcopenia confirmed (37.9%) and that proportion was higher in males than females (43.3% vs. 30.6%, respectively). Males also presented higher proportions of low aBMD and BMC Z-score than females at all sites, except for femoral neck BMC Z-score (63.3% vs. 52.2%, respectively).

Differences in aBMD Z-score at each site according to sarcopenia status

Figure 2 depicts that survivors with sarcopenia confirmed had significantly lower aBMD Z-score than survivors with no sarcopenia at total body (-1.2 [95% CI: -1.5 to -0.8] vs. 0.2 [95% CI: -0.2 to 0.6], P < .001), lumbar spine (-0.7 [95% CI: -1.1 to -0.3] vs. 0.4 [95% CI: 0.0 to 0.8], P < .001), total hip (-0.5 [95% CI: -0.9 to -0.2] vs. 0.4 [95% CI: 0.1 to 0.8], P < .001) and femoral neck (-1.0 [95% CI: -1.4 to -0.6] vs. 0.1 [95% CI: -0.3 to 0.4], P = .001). In comparison to survivors with sarcopenia probable, survivors with sarcopenia confirmed had significantly lower aBMD Z-score at total body (-1.2 [95% CI: -1.5 to -0.8] vs. -0.2 [95% CI: -0.7 to 0.4], P = .009), total hip (-0.5 [95% CI: -0.9 to -0.2] vs. 0.5 [95% CI: -0.1 to 1.0], P = .010) and femoral neck (-1.0 [95% CI: -1.4 to -0.6] vs. 0.1 [95% CI: -0.5 to 0.7], P = .014). No differences were

found between survivors with sarcopenia probable and no sarcopenia (P > .607). After adjusting for calcium intake and total physical activity, results were mostly similar (**Figure S3**). Likewise, when examining same analyses for BMC Z-score, results were consistent (**Figures S4-5**).

Risk of low aBMD Z-score at each site according to sarcopenia status

The risk of low aBMD of survivors with sarcopenia confirmed/probable is presented in **Table 3**. Survivors with sarcopenia confirmed were at higher risk of low aBMD Z-score at the total body (OR: 6.91, 95% CI: 2.31 to 24.15), total hip (OR: 2.98, 95% CI: 1.02 to 9.54) and femoral neck (OR: 4.72, 95% CI: 1.72 to 14.19), than those without sarcopenia. Survivors with sarcopenia probable were at higher risk of low aBMD Z-score at the total body (OR: 4.13, 95% CI: 1.04 to 17.60), than those without sarcopenia. These results, controlled for time from treatment completion, radiotherapy exposure remained the same when calcium intake and total physical activity were additionally included in the models (**Table S2**). Findings were consistent when BMC Z-score outcome variables were used (**Tables S3-4**).

Table 1. Descriptive characteristics of the survivors included in the study.

Characteristics	Total	N	Females	N	Males	N
Sex (female/male, %)	42.2/57.8	116				
Age (years)	12.1 ± 3.3	116	12.2 ± 3.5	49	12.0 ± 3.2	67
Body mass (kg)	46.6 ± 18.0	116	45.2 ± 18.3	49	47.6 ± 17.9	67
Stature (cm)	147.5 ± 17.1	116	145.3 ± 16.0	49	149.0 ± 17.7	67
Body mass index Z-score	0.9 ± 1.1	116	0.8 ± 1.1	49	1.0 ± 1.2	67
Body mass index (categories, %)						
Underweight	3.5	4	6.1	3	1.5	1
Normoweight	61.2	71	65.4	32	58.2	39
Overweight	20.7	24	16.3	8	23.9	16
Obese	14.6	17	12.2	6	16.4	11
Years from peak height velocity	-0.8 ± 2.7	116	0.0 ± 2.9	49	-1.3 ± 2.5	67
Time from treatment completion (years)	5.0 ± 3.8	113	5.2 ± 4.1	48	4.9 ± 3.6	65
Radiotherapy exposure (yes/no, %)	27.6/72.4	116	24.5/75.5	49	29.8/70.2	67
Type of cancer (categories, %)						
Blood	60.9	70	59.2	29	62.1	41
Solid	39.1	45	40.8	20	37.9	25
Calcium intake (mg)	785.5 ± 437.2	116	702.2 ± 388.6	49	846.4 ± 463.0	67
Physical activity (min/day)	297.7 ± 84.0	110	298.1 ± 94.1	48	297.4 ± 76.0	62

Note: Data are presented as mean ± SD or as frequencies (%), as indicated.

Table 2. Distribution of sarcopenia status, age-, sex- and race-specific low areal bone mineral density (aBMD) and bone mineral content (BMC) Z-score.

Characteristics	Total	N	Females	N	Males	N
Muscle strength deficits (%)	56.9	66	59.2	29	55.2	37
Low ALMI Z-score (%)	53.5	62	49.0	24	56.7	38
Sarcopenia status (%)						
No Sarcopenia	43.1	50	40.8	20	44.8	30
Sarcopenia Probable	19.0	22	28.6	14	11.9	8
Sarcopenia Confirmed	37.9	44	30.6	15	43.3	29
Low aBMD Z-score (%)						
Total body (less head)	25.9	30	24.5	12	26.9	18
Lumbar spine	26.7	31	18.4	9	32.8	22
Total hip	20.0	22	14.3	7	22.4	15
Femoral neck	27.6	32	24.5	12	29.9	20
Low BMC Z-score (%)						
Total body (less head)	31.9	37	26.5	13	35.8	24
Lumbar spine	28.5	33	24.5	12	31.3	21
Total hip	18.1	21	16.3	8	19.4	13
Femoral neck	56.9	66	63.3	31	52.2	35

Note: Data are presented as mean ± SD or as frequencies (%), as indicated. Abbreviations: ALMI = appendicular lean mass index; aBMD = areal bone mineral density; BMC = bone mineral content.

Table 3. Odds ratios (95%) for low age-, sex- and race-specific areal bone mineral density (aBMD) Z-score at each site according to sarcopenia status.

	Normal aBMD (%)	Low aBMD (%)	OR	95% CI
Total body (less head)				
No Sarcopenia	44 (89.8)	5 (10.2)	1.00	
Sarcopenia Probable	16 (72.7)	6 (27.3)	**4.13**	**1.04 to 17.60**
Sarcopenia Confirmed	23 (54.8)	19 (45.2)	**6.91**	**2.31 to 24.15**
Lumbar spine				
No Sarcopenia	41 (83.7)	8 (16.3)	1.00	
Sarcopenia Probable	16 (72.7)	6 (27.3)	2.09	0.60 to 7.17
Sarcopenia Confirmed	27 (64.3)	15 (35.7)	2.56	0.95 to 7.27
Total hip				
No Sarcopenia	43 (87.8)	6 (12.2)	1.00	
Sarcopenia Probable	18 (85.7)	3 (14.3)	1.25	0.24 to 5.41
Sarcopenia Confirmed	29 (69.0)	13 (31.0)	**2.98**	**1.02 to 9.54**
Femoral neck				
No Sarcopenia	42 (85.7)	7 (14.3)	1.00	
Sarcopenia Probable	17 (81.0)	4 (19.0)	1.51	0.35 to 5.94
Sarcopenia Confirmed	23 (54.8)	19 (45.2)	**4.72**	**1.72 to 14.19**

Notes: Binary logistic regression (low aBMD identified as Z-score less than -1.0, and normal aBMD identified as Z-score higher than -1.0) were used to estimate odds ratios with 95% confidence intervals. Adjusted models included time from treatment completion (years) and radiotherapy exposure (yes/no). Age-, sex- and race-specific aBMD Z-score at each site are presented using international reference data from the Bone Mineral Density in Childhood Study. Bold values denote statistical significance (*P*-values < .05). Abbreviations: aBMD = areal bone mineral density; CI = confidence interval; OR = odds ratio.

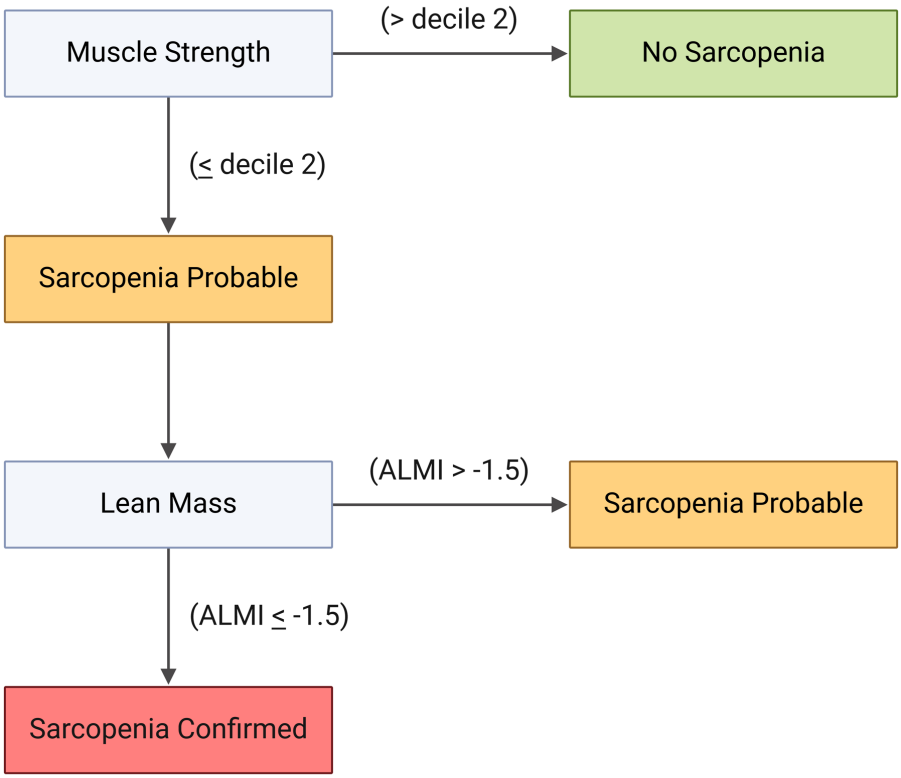

Figure 1. Sarcopenia status classification algorithm for identifying subjects with no sarcopenia, sarcopenia probable or sarcopenia confirmed (following the criteria of the sarcopenia definition stated by the EWGSOP2 [30]). Muscle strength was compared to age- and sex-specific reference values of healthy young population by the FitBack network [28]. Using international reference data from the Bone Mineral Density in Childhood Study [25], age- and sex-specific ALMI Z-score was calculated. Abbreviations: ALMI, appendicular lean mass index.

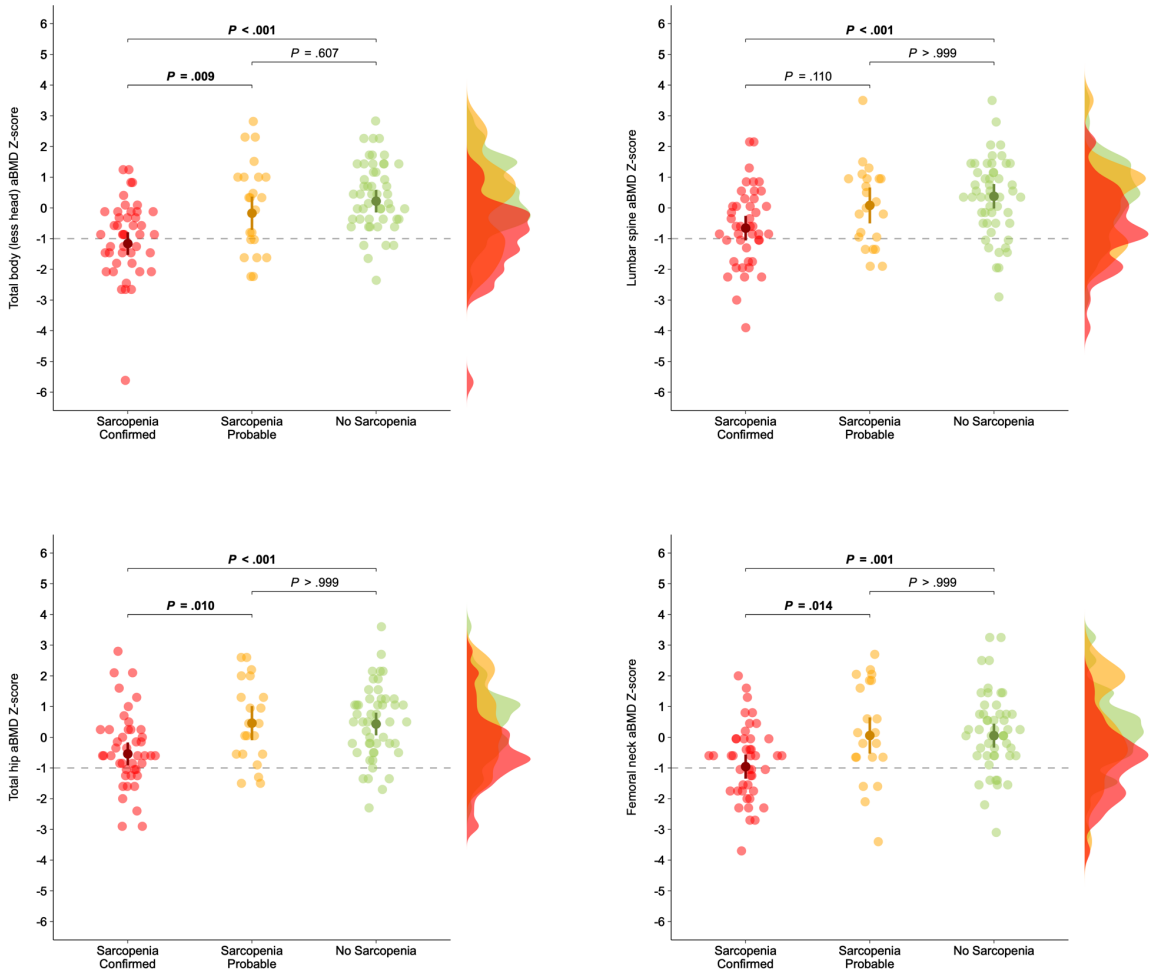

Figure 2. Differences in age-, sex- and race-specific areal bone mineral density (aBMD) Z-score according to sarcopenia status in young pediatric cancer survivors. Data are presented as adjusted means and confidence intervals (95%). Half violin plots show the distribution within sarcopenia status. Significant differences (adjusted P < .05) between sarcopenia status are shown in bold by analysis of covariance. Analyses were adjusted for time from treatment completion to baseline evaluation (years) and radiotherapy exposure (yes/no). Grey dashed line indicates the cut-off point for low areal bone mineral density according to van Atteveld et al. (2019) [3].

Discussion

Over one-third of young pediatric cancer survivors enrolled on this study presented sarcopenia confirmed and had significantly lower aBMD Z-score than survivors with no sarcopenia or sarcopenia probable at all regions. Survivors with sarcopenia confirmed presented higher risk of low aBMD Z-score at total body, total hip and femoral neck, than those without sarcopenia. Previous reports [34-37] describing sarcopenia in young pediatric cancer survivors have not included functional outcomes. In our study, handgrip muscle strength in addition to ALMI via DXA were measured following the criteria of the sarcopenia definition stated by the EWGSOP2 [30]. The importance of including functional outcomes in the definition of sarcopenia is supported by our findings as not all survivors in our study with low ALMI had muscle strength deficits. Moreover, aBMD was not impaired at any site in survivors with low ALMI, but with normal muscle strength.

There are few reports describing concomitant sarcopenia and low aBMD in young pediatric cancer survivors. Previous studies have observed that muscle strength deficits are associated with low aBMD in young [38] and adult pediatric cancer survivors [31], but very few have investigated whether having low ALMI in addition to muscle strength deficits (sarcopenia confirmed) would be associated with low aBMD even shortly after treatment completion. A study led by Guo et al. [39] examined the link between sarcopenia status (measuring both lean mass and ankle dorsiflexion strength) and aBMD in 20 pediatric high-risk neuroblastoma survivors (12.4 $\pm$ 1.6 years). In their study, survivors presented sarcopenia but not low aBMD after a median of nine years from diagnosis (median of 2.8 years old at diagnosis). Their sample size was small and limited to high-risk neuroblastoma survivors, whose treatment exposures likely differ from the exposures in our study population. Our results of coexisting geriatric symptoms are similar to a cohort study of 2,003 adult survivors of pediatric cancer that reported the coexistence of sarcopenia, pre-frailty and frailty (including low aBMD) at a mean age of 33 years [13]. Our findings suggest that sarcopenia and low aBMD coexist soon after completion of therapy. Resistance training-based interventions designed to target both morbidities may prevent frailty and reduce the risk for fractures later in life.

Limitations

Our results should be considered in the context of some potential limitations. Firstly, yet we present results controlling for major potential confounders identified through the DAG methodology (i.e., age, sex, time from treatment completion, radiotherapy exposure, physical activity and calcium intake), residual confounding cannot be disregarded. Secondly, reliance

on aBMD systematically may systematically underestimate aBMD in shorter individuals because bone depth is not accounted for in DXA results. Thirdly, the survivors included in the present study were those who chose to participate in an exercise intervention to improve aBMD, and they may not be representative of all young pediatric cancer survivors.

Public health implications

A myriad of studies have shown that young pediatric cancer survivors are at higher risk of muscle strength deficits, low lean mass and low aBMD [3,6,38]. However, the interconnectedness between these premature complications have not been described together shortly after treatment completion. Given that screening for both age- and sex-specific muscle strength deficits and low lean mass is clinically recommended, our study adds to the current literature that those with impairments should be referred not only for improving muscular weakness, but also to prevent further decline in bone mass. Since sarcopenia and low aBMD are prevalent in adult pediatric cancer survivors [13], early sarcopenia identification and referral for rehabilitation are fundamental. These findings warrant further research based on well-designed randomized controlled trials right after treatment completion.

Conclusion

This study shows that sarcopenia is prevalent in young pediatric cancer survivors and is associated with higher risk of low aBMD Z-score. These results suggest that sarcopenia detection in young cancer survivors at early stages after treatment completion could help survivors to be screened for low aBMD Z-score. Further research is still needed to confirm these findings in larger cohort studies so that they could be included in surveillance guidelines.

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Supplementary material

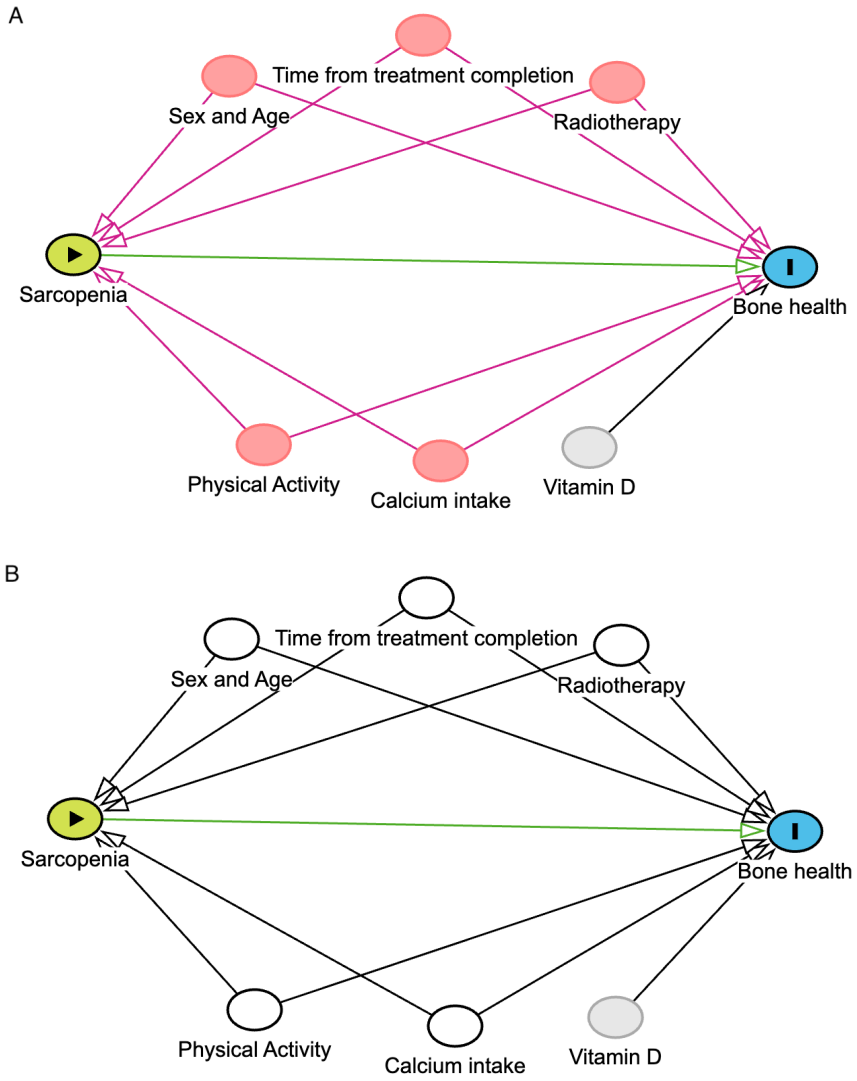

Figure S1. Directed acyclic graph (DAG).

Panel A represents the DAG for the causal structure of the relationship between sarcopenia (exposure, green circle) and bone health (outcome, blue circle). Pink circles indicate ancestor variables of both the exposure and the outcome (sex, age, time from treatment completion, radiotherapy exposure, physical activity and calcium intake). Green arrows indicate "causal" paths, and pink arrows indicate biasing paths.

Panel B represent the DAG after adjusting for the minimum sufficient adjustment set for the total effect (i.e., sex, age, time from treatment completion, radiotherapy exposure, physical activity and calcium intake, now represented with white circles). Note that the biasing paths were completely closed (pink arrows became black arrows, suggesting the correct control for the relevant confounders), and that only the "causal" paths remained opened (both the direct path and the indirect paths, i.e., through mediators).

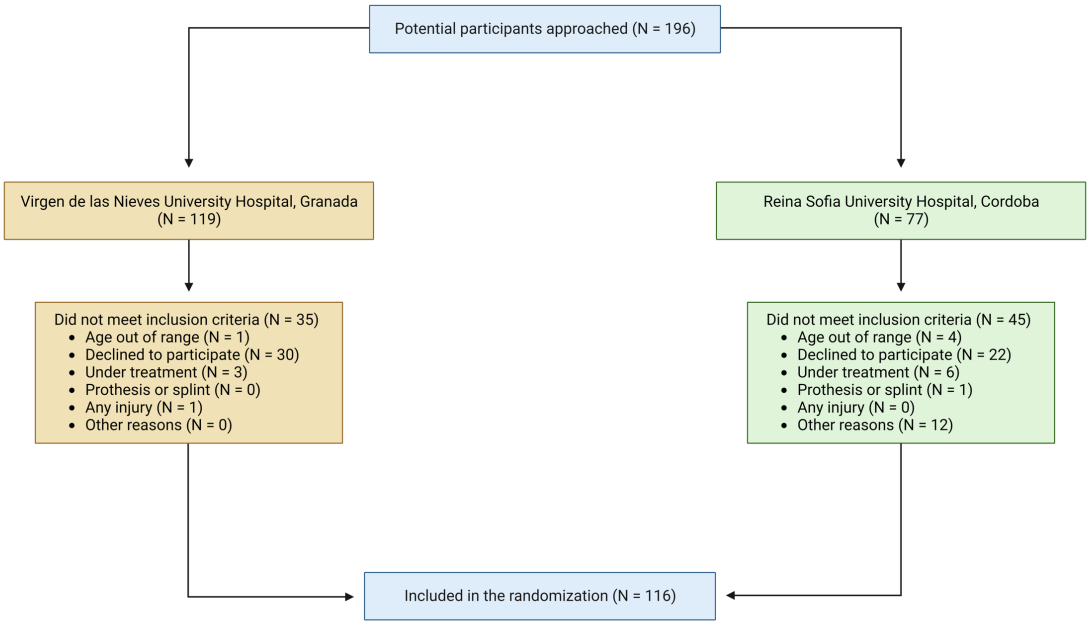

Figure S2. Flow chart.

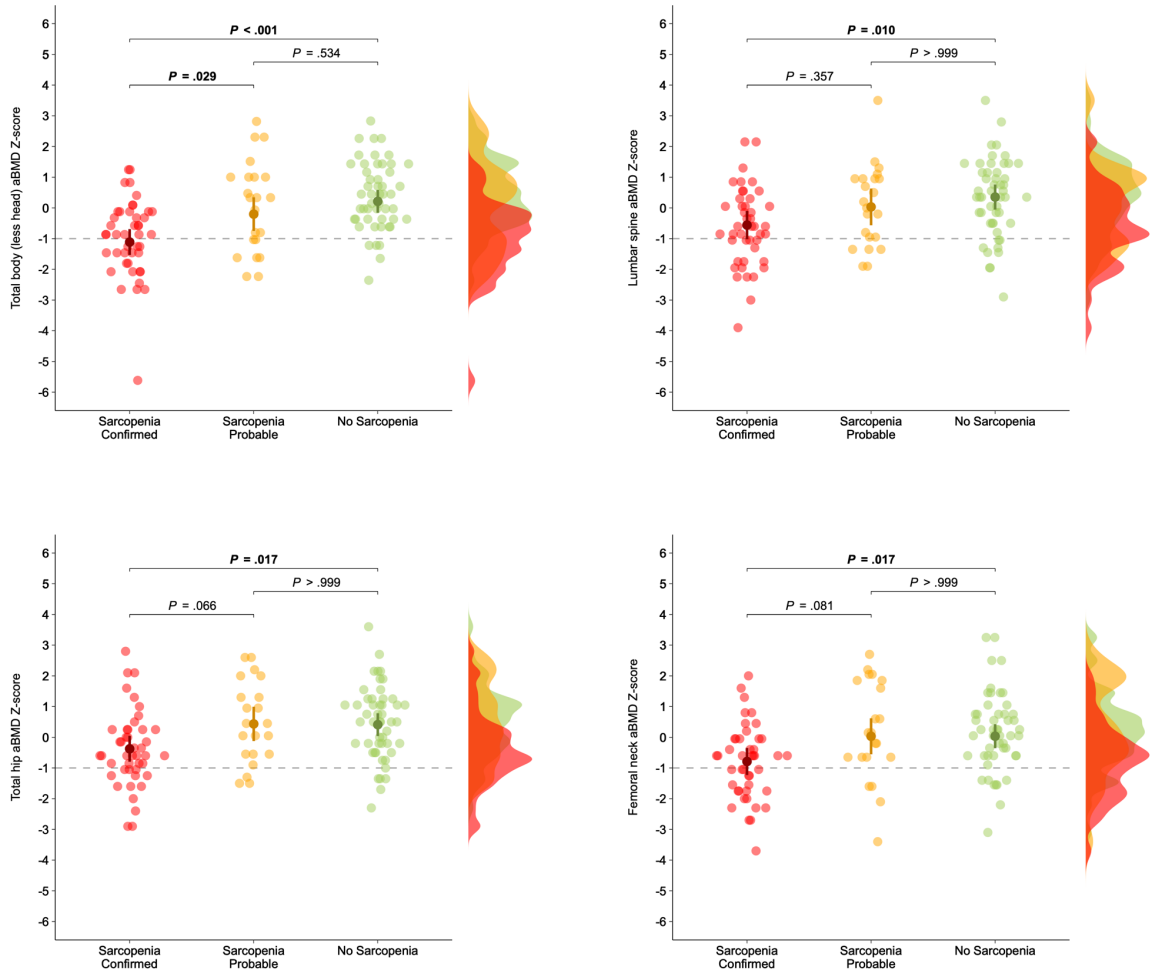

Figure S3. Differences in age-, sex- and race-specific areal bone mineral density (aBMD) Z-score according to sarcopenia status in young pediatric cancer survivors. Data are presented as adjusted means and confidence intervals (95%). Half violin plots show the distribution within sarcopenia status. Significant differences (adjusted P < .05) between sarcopenia status are shown in bold by analysis of covariance. Analyses were adjusted for time from treatment completion to baseline evaluation (years), radiotherapy exposure (yes/no), calcium intake (mg) and total physical activity (min/day). Grey dashed line indicates the cut-off point for low areal bone mineral density according to van Atteveld et al. [(1)].

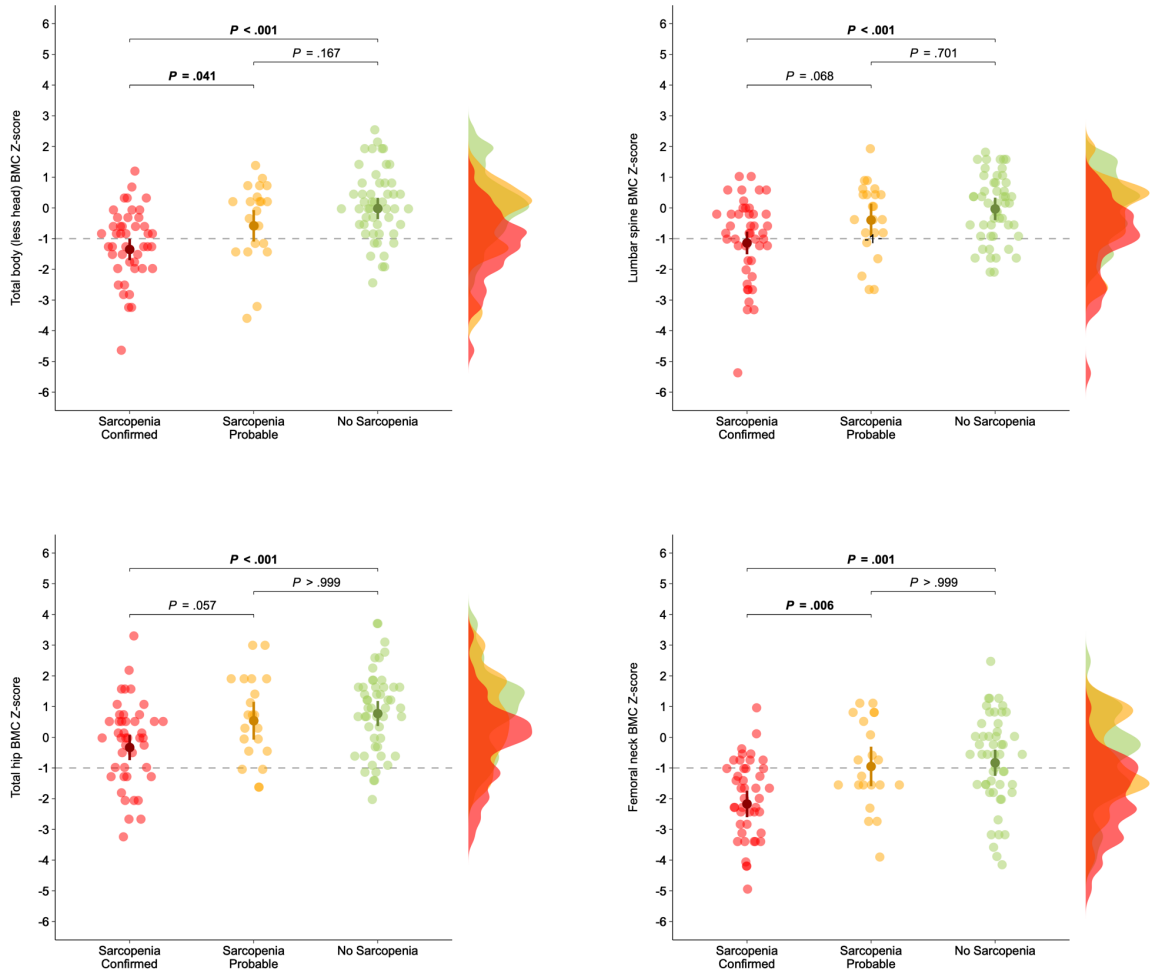

Figure S4. Differences in age-, sex- and race-specific bone mineral content (BMC) Z-score according to sarcopenia status in young pediatric cancer survivors. Data are presented as adjusted means and confidence intervals (95%). Half violin plots show the distribution within sarcopenia status. Significant differences (adjusted P < .05) between sarcopenia status are shown in bold by analysis of covariance. Analyses were adjusted for time from treatment completion to baseline evaluation (years) and radiotherapy exposure (yes/no). Grey dashed line indicates the cut-off point for low bone mineral content according to van Atteveld et al. [(1)].

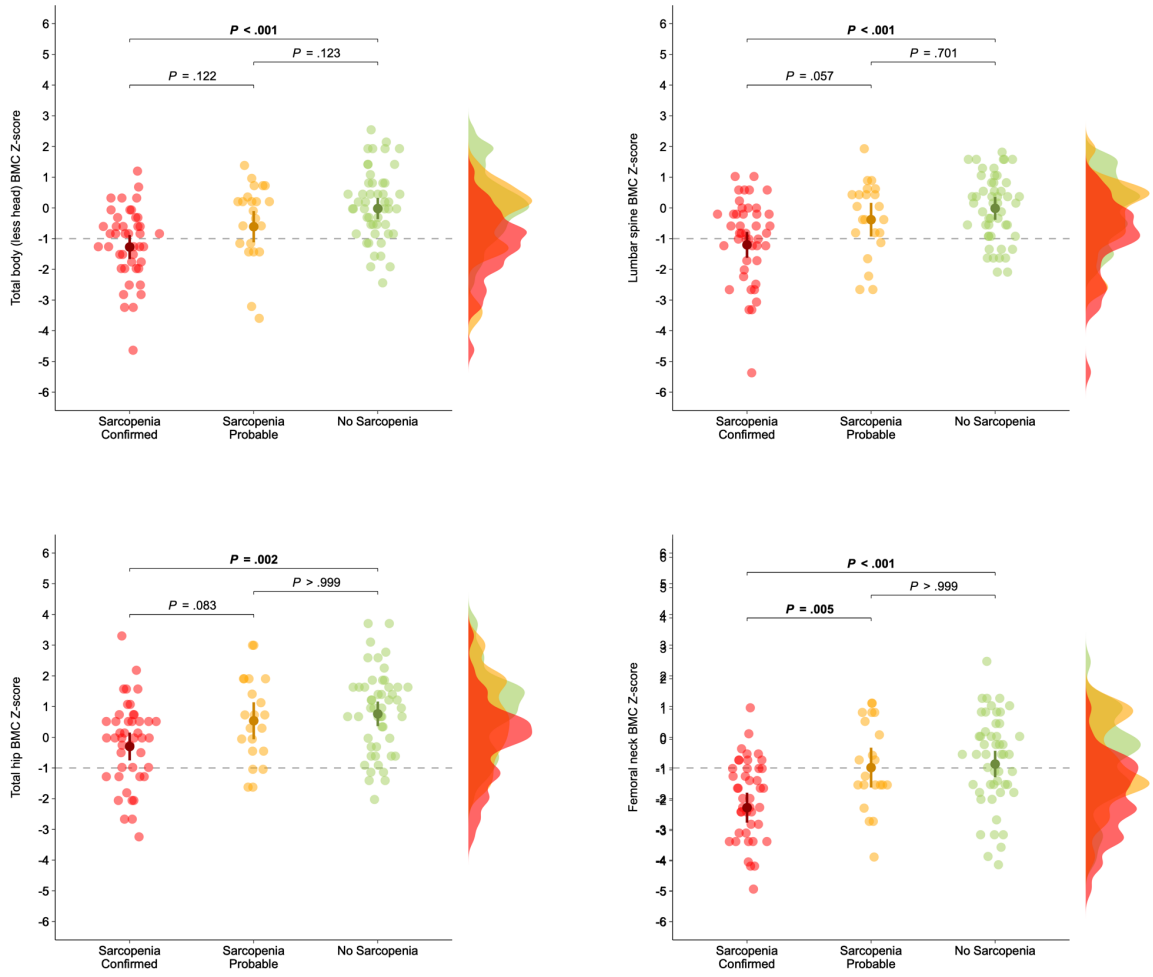

Figure S5. Differences in age-, sex- and race-specific bone mineral content (BMC) Z-score according to sarcopenia status in young pediatric cancer survivors. Data are presented as adjusted means and confidence intervals (95%). Half violin plots show the distribution within sarcopenia status. Significant differences (adjusted P < .05) between sarcopenia status are shown in bold by analysis of covariance. Analyses were adjusted for time from treatment completion to baseline evaluation (years), radiotherapy exposure (yes/no), calcium intake (mg) and total physical activity (min/day). Grey dashed line indicates the cut-off point for low bone mineral content according to van Atteveld et al. [(1)].

Table S1. STROBE Statement-Checklist of items that should be included in reports of *cross-sectional studies.*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	215
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	215
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	216
Objectives	3	State specific objectives, including any prespecified hypotheses	216
Methods			
Study design	4	Present key elements of study design early in the paper	216-217
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	216-217
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	216-217
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	217-219
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	217-219
Bias	9	Describe any efforts to address potential sources of bias	219-220
Study size	10	Explain how the study size was arrived at	216-217
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	217-219
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	219-220
		(*b*) Describe any methods used to examine subgroups and interactions	219-220
		(*c*) Explain how missing data were addressed	219-220
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	219-220
		(*e*) Describe any sensitivity analyses	219-220

		Results	
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure S2
		(b) Give reasons for non-participation at each stage	Figure S2
		(c) Consider use of a flow diagram	Figure S2
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1-2 and Figure S1
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1-2
Outcome data	15	Report numbers of outcome events or summary measures	Table 2 and Figure S2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2, Tables S3-5, Figure 2 and Figures S3-5
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	220-221
		Discussion	
Key results	18	Summarise key results with reference to study objectives	227
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	227-228
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	228
Generalisability	21	Discuss the generalisability (external validity) of the study results	227-228
		Other information	

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Table S2. Odds ratios (95%) of low age-, sex- and race-specific areal bone mineral density (aBMD) Z-score at each site according to sarcopenia status.

	Normal aBMD (%)	Low aBMD (%)	OR	95% CI
Total body (less head)				
No Sarcopenia	44 (89.8)	5 (10.2)	1.00	
Sarcopenia Probable	16 (72.7)	6 (27.3)	**4.08**	**1.00 to 17.66**
Sarcopenia Confirmed	20 (54.1)	17 (45.9)	**6.54**	**2.02 to 24.43**
Lumbar spine				
No Sarcopenia	41 (83.7)	8 (16.3)	1.00	
Sarcopenia Probable	16 (72.7)	6 (27.3)	2.25	0.63 to 7.94
Sarcopenia Confirmed	24 (64.9)	13 (35.1)	2.05	0.70 to 6.24
Total hip				
No Sarcopenia	43 (87.8)	6 (12.2)	1.00	
Sarcopenia Probable	18 (85.7)	3 (14.3)	1.24	0.23 to 5.58
Sarcopenia Confirmed	25 (67.6)	12 (32.4)	2.56	0.79 to 8.83
Femoral neck				
No Sarcopenia	42 (85.7)	7 (14.3)	1.00	
Sarcopenia Probable	17 (81.0)	4 (19.0)	1.49	0.33 to 6.09
Sarcopenia Confirmed	20 (54.1)	17 (45.9)	**4.46**	**1.47 to 14.69**

Notes: Binary logistic regression (low BMC identified as Z-score less than -1.0, and normal BMC identified as Z-score higher than -1.0) were used to estimate odds ratios with 95% confidence intervals. Adjusted models included time from treatment completion (years), radiotherapy exposure (yes/no), calcium intake (mg) and total physical activity (min/day). Age-, sex- and race-specific aBMD Z-score at each site are presented using international reference data from the Bone Mineral Density in Childhood Study [(2)]. Bold values denote statistical significance (*P*-values < .05). Abbreviations: aBMD = areal bone mineral density; CI = confidence interval; OR = odds ratio.

Table S3. Odds ratios (95%) of low age-, sex- and race-specific bone mineral content (BMC) Z-score at each site according to sarcopenia status.

	Normal BMC (%)	Low BMC (%)	OR	95% CI
Total body (less head)				
No Sarcopenia	41 (83.7)	8 (16.3)	1.00	
Sarcopenia Probable	15 (68.2)	7 (31.8)	2.81	0.83 to 9.72
Sarcopenia Confirmed	20 (47.6)	22 (52.4)	**5.14**	**1.95 to 14.66**
Lumbar spine				
No Sarcopenia	40 (81.6)	9 (18.4)	1.00	
Sarcopenia Probable	17 (77.3)	5 (22.7)	1.28	0.35 to 4.32
Sarcopenia Confirmed	24 (57.1)	18 (42.9)	**3.49**	**1.35 to 9.66**
Total hip				
No Sarcopenia	43 (87.8)	6 (12.2)	1.00	
Sarcopenia Probable	18 (85.7)	3 (14.3)	1.21	0.23 to 5.19
Sarcopenia Confirmed	30 (71.4)	12 (28.6)	2.79	0.95 to 9.01
Femoral neck				
No Sarcopenia	28 (57.1)	21 (42.9)	1.00	
Sarcopenia Probable	10 (47.6)	11 (52.4)	1.44	0.50 to 4.20
Sarcopenia Confirmed	8 (19.0)	34 (81.0)	**6.60**	**2.47 to 19.68**

Notes: Binary logistic regression (low BMC identified as Z-score less than -1.0, and normal BMC identified as Z-score higher than -1.0) were used to estimate odds ratios with 95% confidence intervals. Adjusted models included time from treatment completion (years) and radiotherapy exposure (yes/no). Age-, sex- and race-specific BMC Z-score at each site are presented using international reference data from the Bone Mineral Density in Childhood Study [2]. Bold values denote statistical significance (*P*-values < .05). Abbreviations: aBMD = areal bone mineral density; CI = confidence interval; OR = odds ratio.

Table S4. Odds ratios (95%) of low age-, sex- and race-specific bone mineral content (BMC) Z-score at each site according to sarcopenia status.

	Normal BMC (%)	Low BMC (%)	OR	95% CI
Total body (less head)				
No Sarcopenia	41 (83.7)	8 (16.3)	1.00	
Sarcopenia Probable	15 (68.2)	7 (31.8)	2.77	0.77 to 10.08
Sarcopenia Confirmed	17 (45.9)	20 (54.1)	**4.83**	**1.66 to 15.13**
Lumbar spine				
No Sarcopenia	40 (81.6)	9 (18.4)	1.00	
Sarcopenia Probable	17 (77.3)	5 (22.7)	1.28	0.34 to 4.36
Sarcopenia Confirmed	20 (54.1)	17 (45.9)	**4.27**	**1.50 to 13.24**
Total hip				
No Sarcopenia	43 (87.8)	6 (12.2)	1.00	
Sarcopenia Probable	18 (85.7)	3 (14.3)	1.02	0.18 to 4.68
Sarcopenia Confirmed	25 (67.6)	12 (32.4)	2.51	0.76 to 8.94
Femoral neck				
No Sarcopenia	28 (57.1)	21 (42.9)	1.00	
Sarcopenia Probable	10 (47.6)	11 (52.4)	1.44	0.49 to 4.28
Sarcopenia Confirmed	8 (21.6)	29 (78.4)	**7.44**	**2.58 to 24.25**

Notes: Binary logistic regression (low BMC identified as Z-score less than -1.0, and normal BMC identified as Z-score higher than -1.0) were used to estimate odds ratios with 95% confidence intervals. Adjusted models included time from treatment completion (years), radiotherapy exposure (yes/no), calcium intake (mg) and total physical activity (min/day). Age-, sex- and race-specific BMC Z-score at each site are presented using international reference data from the Bone Mineral Density in Childhood Study [(2)]. Bold values denote statistical significance (*P*-values < .05). Abbreviations: aBMD = areal bone mineral density; CI = confidence interval; OR = odds ratio.

References

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Chapter 10. Effects of a 9-month online resistance exercise intervention on bone health in young pediatric cancer survivors: A Randomized Controlled Trial

Abstract

Purpose. Pediatric cancer survivors remain at risk of low areal bone mineral density (aBMD). Resistance exercise of high impact loading is known to successfully improve aBMD in healthy children. The aim of this randomized controlled trial was to investigate the effects of a 9-month online resistance exercise intervention on femoral neck aBMD Z-score (primary outcome), and on other markers of bone health including aBMD and bone mineral content [BMC] Z-score (secondary outcomes) in young pediatric cancer survivors.

Methods. A total of 116 survivors aged 6 to 18 years (12.1±3.3 years old; 42% female) were randomized to exercise (N=58) or control groups (N=58), and were included in the intention-to-treat analysis. All participants received diet counselling on calcium and vitamin D before the intervention. The exercise group performed a 9-month periodized resistance exercise intervention of high impact loading (three to four days/week during 10-20 min/session) at home. The primary (femoral neck aBMD [g/cm^2]) and secondary outcomes (aBMD and BMC [g]) were measured by Dual-energy X-ray absorptiometry at hip regions (femoral neck and total hip), total body (less head) and lumbar spine (mean of L1-L4) at baseline and 9-month post-intervention.

Results. We could not detect statistically significant differences between groups on femoral neck aBMD Z-score (difference between groups: -0.04 SD, 95% CI: -0.22 to 0.15, P = .706). Regarding secondary bone outcomes, the exercise intervention showed small-sized effects on total hip BMC Z-score (difference between groups: 0.45 SD, 95% CI: 0.02 to 0.87, P = .039). There were no other between-group statistically significant differences on the rest of aBMD or BMC Z-score outcomes. No major, mild or minor adverse events were reported.

Conclusion. A 9-month online resistance exercise intervention of high impact loading does not increase femoral neck aBMD Z-score, yet it induces improvements at the hip region in young pediatric cancer survivors. Future studies are needed to confirm whether supervised full-body resistance exercise interventions of high impact loading can improve bone health at femoral neck aBMD Z-score and other key regions in this population.

Introduction

The 5-year survival rate for all pediatric cancer diagnoses combined has substantially increased over the last half-century [1] from 58% to 85% for children and from 68% to 87% for adolescents [2]. However, required treatment to cure cancer at such a young age increase the risk of later health-related complications [3], including low areal bone mineral density (aBMD) [4], which has been reported in up to two-thirds of survivors [5]. Thus, the identification of strategies that counteract bone loss in this population is key to reduce the increased risk of osteopenia and/or osteoporosis in adulthood [6,7], which may well lead to lower risk of fractures [8].

Bisphosphonate treatment could successfully improve aBMD in pediatric cancer survivors [9], but may also cause some potential side effects such as fever, vomiting, and abdominal, muscle or bone pain [10]. Non-pharmacological treatment, such as exercise [11], are known to successfully improve aBMD in healthy children and if the training principles (i.e., frequency, intensity, time, type, volume and progression) are appropriately followed, they could also be beneficial for young pediatric cancer survivors. Nevertheless, there is a lack of randomized controlled trials (RCTs) targeting bone outcomes in this population [12]. Most of the interventions in previous studies, evaluating bone outcomes, have not been specifically designed to improve these outcomes and hence, they were not effective [12]. Reasons for the lack of success of these interventions may include low frequency and volume [13], short trial duration (i.e., three months) [13,14], inclusion of aerobic/non-osteogenic exercises (i.e., cycling, swimming) [15] or microgravity environments (i.e., swimming pools) [14]. In addition, recent evidence underlined the need for post-treatment exercise interventions, as the frequency and intensity of exercise required to improve bone outcomes may have been too high to be achieved during treatment [16]. Therefore, exercise based RCTs specifically designed to improve bone health are needed after pediatric cancer.

The aim of this randomized controlled trial was to investigate the effects of a 9-month online resistance exercise intervention on femoral neck aBMD Z-score (primary outcome), and on other markers of bone health including aBMD and bone mineral content [BMC] Z-score (secondary outcomes) in young pediatric cancer survivors. We hypothesized that the intervention would be an efficacious stimulus on bone health in this population.

Methods

Design

Parallel-group REBOTA-Ex RCT (within iBoneFIT project) approved by the Ethics Committee on Human Research of Regional Government of Andalusia (Reference: 4500, December 2019), followed the ethical guidelines of the Declaration of Helsinki (revised version 2013) and was registered in isrctn.com (Reference: isrctn61195625, 2 April 2020) [17]. Consolidated Standards of Reporting Trials (CONSORT) reporting guideline were followed (**Table S1**). Finally, all these research processes have been conducted under the premises of the Singapore Statement on Research Integrity [18].

Participants

Young pediatric cancer survivors aged from 6 to 18 years, diagnosed at least one year prior to enrolment, with previous exposure to radiotherapy and/or chemotherapy and not currently receiving treatments for cancer were recruited from the Units of Pediatric Oncology and Hematology of the 'Virgen de las Nieves' (Granada) and 'Reina Sofia' (Cordoba) University Hospitals. Data collection occurred in two waves due to COVID-19 restrictions: 1) October 2020 to February 2021; and 2) December 2021 to March 2022. Sample size was calculated based on a key outcome in the diagnosis of osteoporosis (i.e., femoral neck aBMD) [19]. Considering an expected effect size of 0.25 for the change in femoral neck aBMD, an α level of 0.05 and a power of 80%, a minimum of 116 participants was required (exercise group = 58 and control group = 58). This also included a 20% extra for occasional losses and refusals, and 10% for multivariable analyses. In addition, the sample size was calculated considering sub-group analysis by age groups (6-11 and 12-18 years), but this was not finally performed as primary and secondary outcomes (Z-score) were calculated accounting for age, in addition to sex and race.

Randomization and Blinding

After completion of baseline testing, participants were assigned using SAS software (version 9.1, SAS Institute Inc.) to the exercise or control group (1:1) with block sizes of age and sex by an external partner (VMV) who was independent of the participant recruitment and enrolment process. This randomization process was carried out before baseline assessment. The outcome assessors were blinded to the group allocation, but participants, due to the nature of the exercise intervention, could not be blinded to group assignments.

Intervention

The exercise group performed a periodized resistance exercise intervention of high impact loading at home. The sessions were pre-recorded and individually delivered to participants every other week. This enabled participants to accomplish the number of sessions on demand throughout the week (preferably on Mondays, Wednesdays and Fridays; or Mondays, Tuesdays, Thursdays and Fridays) as well as increase parental involvement for this matter when needed. The total volume was 7296 squat/jumps (2000 squats + 5296 jumps) in 136 sessions over nine months during 10-20 min/session. The intensity progressively increased in volume (three to four sets, 10 to 20 repetitions and three to four sessions per week) within the intervention phases. The intervention was divided in three phases of different durations and impact loadings. The first phase corresponded to the first eight weeks of the exercise intervention. Participants performed body mass-based squats and the volume was progressively increased by modifying the number of repetitions and sets per session. The second phase lasted 12 weeks and participants performed squat jumps. In this phase, the volume was progressively increased by modifying the number of repetitions, sets per day and sessions per week. The third phase was the longest phase of the exercise intervention with 16 weeks. Participants performed countermovement jumps and the volume of this phase was progressively increased by modifying the number of repetitions, sets per day and sessions per week. The exercise intervention included five behavior change techniques (i.e., action planning and goal setting, providing instructions and demonstrations of how to perform the behavior, self-monitoring of behavior, providing feedback on performance and information about health consequences) and a gamification design (i.e., points and rankings) to maintain participants' interest and adherence.

Educational leaflets and infographics based on the current recommendations of calcium and vitamin D [20] were delivered to all participants before the intervention. Participants in the control group continued their usual routines and once the study was completed, we offered to them the same online resistance exercise intervention.

Adherence

The intervention was remotely monitored using a diary that was given at baseline. The minimum adherence allowed at each phase of the intervention was 50%, but the overall adherence after nine months had to reach 70% (completion of 95/136 sessions). If a participant did not complete 70% of the intervention by the end of the nine months, but could reach 70% within two additional weeks, the exercise intervention was extended. To encourage adherence, participants were contacted monthly by the research staff to provide the diary with the number

of completed sessions, and were offered problem-solving strategies if they had difficulties performing the resistance exercise sessions major, mild or minor adverse events. Parental involvement was requested for this matter when needed to motivate participants to engage in the intervention and to come to the lab facilities to go through all the assessments. Actual adherence was determined as the percentage of performed sessions at study completion from those that were prescribed.

Outcomes

The primary (femoral neck aBMD [g/cm^2]) and secondary outcomes (aBMD and BMC [g]) were measured by Dual-energy X-ray absorptiometry (DXA) at hip regions (femoral neck and total hip), total body (less head) and lumbar spine (mean of L1–L4) at baseline and 9-month follow-up. Participants were evaluated using a single DXA scanner (Hologic Series Discovery QDR, Bedford, MA, USA) and analyzed by APEX software (version 4.0.2). The device was calibrated each day using a lumbar spine phantom. Participants were asked to remain still and scanned in the supine position according to the International Society of Clinical Densitometry [(19)]. A single licensed and experienced researcher analyzed all DXA scans. DXA coefficient of variation in pediatric population ranges between 1.0 and 2.9%, depending on the region [(21)]. Using international reference data from the Bone Mineral Density in Childhood Study [(22)], age-, sex- and race-specific aBMD and BMC Z-score at femoral neck, total hip, total body and lumbar spine were calculated.

Demographic, Anthropometric and Clinical Variables

Body mass (kg) was evaluated with an electronic scale (SECA 861, Hamburg, Germany) with an accuracy of 100 g. Stature (cm) was assessed using a precision stadiometer (SECA 225, Hamburg, Germany) to the nearest 0.1 cm. Body mass index was calculated as body mass (kg)/stature (m2). Additionally, age- and sex-specific body mass index Z-score and categories were calculated using international reference data for pediatric population according to the World Obesity Federation [(23)]. Somatic maturity was measured using the prediction of years before or after peak height velocity using validated algorithms for boys and girls [(24)]. Vitamin D status was estimated by a validated food-frequency questionnaire based on three questions regarding sun exposure during the last year (yes/no), use of tanning booth (yes/no) and the number of glasses of milk per day (two or more glasses were considered as yes) [(25)]. Using the threshold of two negative responses out of the three questions for these habits proposed by Bolek-Berquist et al. [(25)], we identified participants with vitamin D deficiency. Medical records

were used to retrieve information regarding serum calcium (mg/dL), diagnosis, time from treatment completion to baseline data collection and treatment exposure (radiotherapy, chemotherapy and/or surgery, alone or in combination).

Statistical Analysis

The analysis of primary and secondary outcomes were performed using an intention-to-treat approach including all participants as they were originally randomized in this efficacy RCT, as well as a per-protocol approach (Supplementary material). Missing data were not imputed [26,27] since baseline values were considered as part of the outcome vectors and all participants with at least one evaluation were included in the analyses [28]. Missing data in primary and secondary outcomes were the result of participants withdrawing from the study before completion and were assumed to be missing at random. The per-protocol analysis criteria included: (i) completion of both outcome assessments at baseline and post-intervention, and (ii) minimum adherence with the exercise intervention.

Intervention effects on primary and secondary outcomes were analyzed using a constrained baseline longitudinal analysis via a linear mixed model [28]. The model included fixed effects for time (two levels), treatment (coded 0 for all groups at baseline and coded 0 or 1 at follow-up for the exercise and control groups, respectively), as well as the unique participant identifier as a random effect. Data are presented as within-group mean changes and differences between-group mean changes with 95% confidence intervals unless mentioned. The LMMstar package was used to construct the linear mixed models for the analysis [29]. Statistical analyses were performed using the statistical software R version 4.4.0 (R Foundation for Statistical Computing). All P-values were from 2-sided tests and results were deemed statistically significant at $P < .05$.

Intervention effects assessments were based not only on statistical significance but also on a practical benefit approach emphasizing and reporting unadjusted values that are intuitive to human judgment and readily replicable considering the design and methods used in this study [30,31]. Results were not stratified by sex since primary and secondary outcomes were calculated accounting for sex, in addition to age and race.

Results

Among the 196 participants screened, 116 consented (recruitment rate, 59.2%) (**Figure 1**). In the exercise group, 13 participants did not complete the postintervention bone health evaluation and nine did not accomplish the minimum adherence allowed. In the control group, four

participants did not complete the postintervention bone health evaluation. The mean (SD) adherence in the exercise group was 92.3% (11.1) in the first phase, 87.7% (12.6) in the second phase and 69.4% (26.3) in the third phase (total mean [SD] adherence was 83.1% [12.7]). A total of 116 participants were therefore included in the intention-to-treat analysis, and according to the per-protocol analysis criteria, 90 participants (77.6%) were included in this analysis.

Baseline Characteristics

Descriptive participants' characteristics at baseline are shown in **Table 1**. Of the included participants, 58 were randomized to the exercise group (mean [SD] age was 11.7 [3.2] years and 37.9% were female) and 58 were randomized to the control group (mean [SD] age was 12.5 [3.5] years and 46.6% were female). All participants were of Caucasian ethnicity and most of them were normoweight (61.2%). In the exercise and control groups, mean years from peak height velocity were -1.0 (2.6) and -0.5 (2.8), mean time from treatment completion was 4.5 (3.5) and 5.6 (4.0) years, and the proportion of participants exposed to radiotherapy was the same in both groups (27.6%). Moreover, acute lymphoblastic leukemia was the most predominant cancer type (39.7% and 37.9% in the exercise and control groups, respectively) [**Table S2**]).

Changes in Primary and Secondary Outcomes

Table 2 presents the within-group changes and between-group differences of changes in primary and secondary outcomes. We could not detect statistically significant effects on femoral neck aBMD Z-score (difference between groups: -0.04 SD, 95% CI: -0.22 to 0.15, P = .706). At total hip, the difference between groups was 0.26 SD (95% CI: 0.00 to 0.52, P = .054). However, the exercise intervention showed small-sized effects on total hip BMC Z-score (difference between groups: 0.45 SD, 95% CI: 0.02 to 0.87, P = .039). We could not observe statistically significant effects on the rest of BMC Z-score outcomes. Compared to the control group, the exercise group showed a change at femoral neck BMC Z-score of 0.30 SD (95% CI: -0.13 to 0.73, P = .168), at total body BMC Z-score of 0.14 SD (95% CI: -0.06 to 0.33, P = .171) and at lumbar spine BMC Z-score of 0.15 SD (95% CI: -0.04 to 0.34, P = .124). Estimated means at constrained baseline and 9-month follow-up in the aBMD and BMC Z-score outcomes are presented in **Figure 2**. Raw individual changes of total hip and femoral neck aBMD and BMC Z-score from baseline to 9-month follow-up are shown in **Figures 3** and **4**,

respectively. The aBMD and BMC Z-score outcomes at baseline and nine months can be found in **Table S3**.

For per-protocol analysis, the findings on aBMD Z-score outcomes were similar (**Table S4**). Using this approach, estimated means at constrained baseline and 9-month follow-up in the aBMD Z-score outcomes and raw individual changes of total hip and femoral neck aBMD Z-score from baseline to 9-month follow-up are shown in **Figures S1** and **S2**, respectively. The per-protocol analysis showed that the exercise intervention had small-sized effects on femoral neck BMC Z-score (difference between groups: 0.48 SD (95% CI: 0.02 to 0.94, P = .043). We could not observe statistically significant effects on the rest of BMC Z-score outcomes as shown in **Table S4**. Compared to the control group, the exercise group showed a change at total hip BMC Z-score of 0.45 SD (95% CI: -0.01 to 0.92, P = .057), at total body BMC Z-score of 0.21 SD (95% CI: -0.01 to 0.42, P = .058) and at lumbar spine BMC Z-score of 0.21 SD (95% CI: 0.00 to 0.42, P = .050). For per-protocol analysis, estimated means at constrained baseline and 9-month follow-up in the BMC Z-score outcomes are also presented in **Figure S1**. Raw individual changes of total hip and femoral neck BMC Z-score from baseline to 9-month follow-up using per-protocol analysis are shown in **Figure S3**.The aBMD and BMC Z-score outcomes, using per-protocol analysis, at baseline and 9-month can be found in **Table S5**.

Table 1. Descriptive characteristics at baseline of the survivors included in the study.

	Total	N	Intervention	N	Control	N
Sex (female, %)	42.2	116	37.9	58	46.6	58
Age (years)	12.1 (3.3)	116	11.7 (3.2)	58	12.5 (3.5)	58
Body mass (kg)	46.6 (18.0)	116	46.9 (17.9)	58	46.3 (18.3)	58
Stature (cm)	147.5 (17.1)	116	147.2 (16.7)	58	147.7 (17.6)	58
Body mass index Z-score	0.9 (1.1)	116	1.0 (1.2)	58	0.8 (1.1)	58
Body mass index (categories, %)						
Underweight	3.5	4	3.4	2	3.4	2
Normoweight	61.2	71	55.2	32	67.2	39
Overweight	20.7	24	24.1	14	17.2	10
Obesity	14.6	17	17.2	10	12.1	7
Years from peak height velocity	-0.8 (2.7)	116	-1.0 (2.6)	58	-0.5 (2.8)	58
Vitamin D deficiency (yes, %)	53.2	108	50.0	53	56.4	55
Calcium intake (mg/dL)	9.8 (0.5)	103	9.8 (0.5)	40	9.9 (0.5)	50
Time from cancer treatment completion (years)	5.0 (3.8)	113	4.5 (3.5)	57	5.6 (4.0)	56
Radiotherapy exposure (yes, %)	27.6	116	27.6	58	27.6	58
aBMD Z-score						
Femoral neck	-0.2 (1.4)	115	-0.1 (1.5)	58	-0.3 (1.3)	57
Total hip	0.1 (1.3)	115	0.2 (1.3)	58	0.1 (1.3)	57
Total body (less head)	-0.2 (1.4)	116	0.0 (1.4)	58	-0.4 (1.4)	58
Lumbar spine	-0.1 (1.3)	116	0.1 (1.2)	58	-0.3 (1.4)	58
BMC Z-score						
Femoral neck	-1.3 (1.5)	115	-1.2 (1.5)	58	-1.4 (1.5)	57
Total hip	0.4 (1.4)	115	0.5 (1.4)	58	0.3 (1.5)	57
Total body (less head)	-0.5 (1.3)	116	-0.3 (1.1)	58	-0.7 (1.4)	58
Lumbar spine	-0.5 (1.3)	116	-0.2 (1.0)	58	-0.7 (1.5)	58

Data are presented as mean (standard deviation) or as frequencies (percentages), as indicated. Age- and sex-specific BMI Z-score and categories are presented using international reference data for pediatric population according to the International Obesity Task Force [22]. Age-, sex-, and race-specific aBMD and BMC Z-scores at each site are also presented using international reference data from the Bone Mineral Density in Childhood Study [21]. Abbreviations: aBMD, areal bone mineral density; BMC, bone mineral content.

Table 2. Within-group changes (baseline to nine months) and between-group differences (intervention vs. control) in the aBMD and BMC Z-score outcomes.

	Intervention		Control		Between-group Differences		
	Change (95% CI)	Change %[Ψ]	Change (95% CI)	Change %[Ψ]	MD (95% CI)	Effect size	*P*[†]
aBMD Z-score							
Femoral neck	0.11 (-0.05 to 0.28)	4.11	0.15 (0.00 to 0.30)	5.48	-0.04 (-0.22 to 0.15)	-0.08	.706
Total hip	0.22 (-0.01 to 0.46)	6.10	-0.03 (-0.25 to 0.18)	-3.66	0.26 (0.00 to 0.52)	0.35	.054
Total body (less head)	0.03 (-0.16 to 0.23)	3.80	-0.06 (-0.24 to 0.12)	-3.80	0.09 (-0.13 to 0.31)	0.15	.422
Lumbar spine	-0.05 (-0.19 to 0.08)	-4.11	-0.02 (-0.14 to 0.10)	-4.11	-0.04 (-0.19 to 0.12)	-0.07	.642
BMC Z-score							
Femoral neck	0.30 (-0.08 to 0.69)	10.51	0.00 (-0.36 to 0.36)	7.25	0.30 (-0.13 to 0.73)	0.26	.168
Total hip	0.39 (0.00 to 0.77)	14.83	-0.06 (-0.42 to 0.30)	-8.66	0.45 (0.02 to 0.87)	0.38	**.039**
Total body (less head)	0.10 (-0.07 to 0.27)	8.52	-0.04 (-0.20 to 0.12)	-7.08	0.14 (-0.06 to 0.33)	0.26	.171
Lumbar spine	0.11 (-0.06 to 0.28)	9.21	-0.04 (-0.19 to 0.12)	-7.07	0.15 (-0.04 to 0.34)	0.28	.124

Results are presented as mean change from baseline for each group and as mean difference between groups change. Data were analyzed using a constrained baseline longitudinal mixed model adjusted for baseline differences between groups. Age-, sex-, and race-specific aBMD and BMC Z-scores at each site are presented using international reference data from the Bone Mineral Density in Childhood Study [(21)]. Effect sizes were calculated following Cohen's d formula. Abbreviations: aBMD, areal bone mineral density; BMC, bone mineral content; MD, mean difference.

[Ψ] Change percentage was calculated from raw values (g/cm^2 or g).

[†] P-values showed between-group differences on the aBMD and BMC Z-score outcomes.

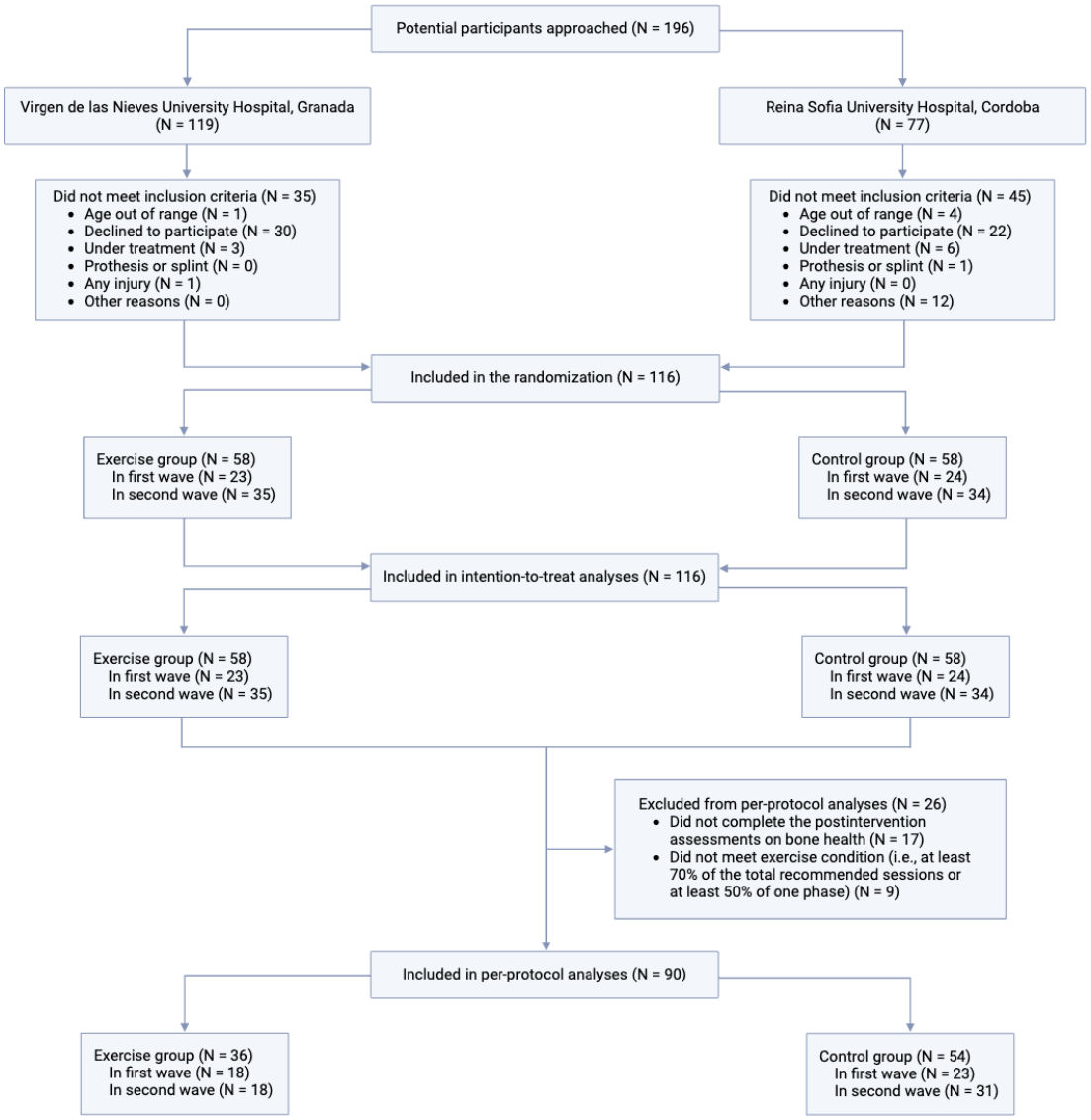

Figure 1. Flow chart of participants.

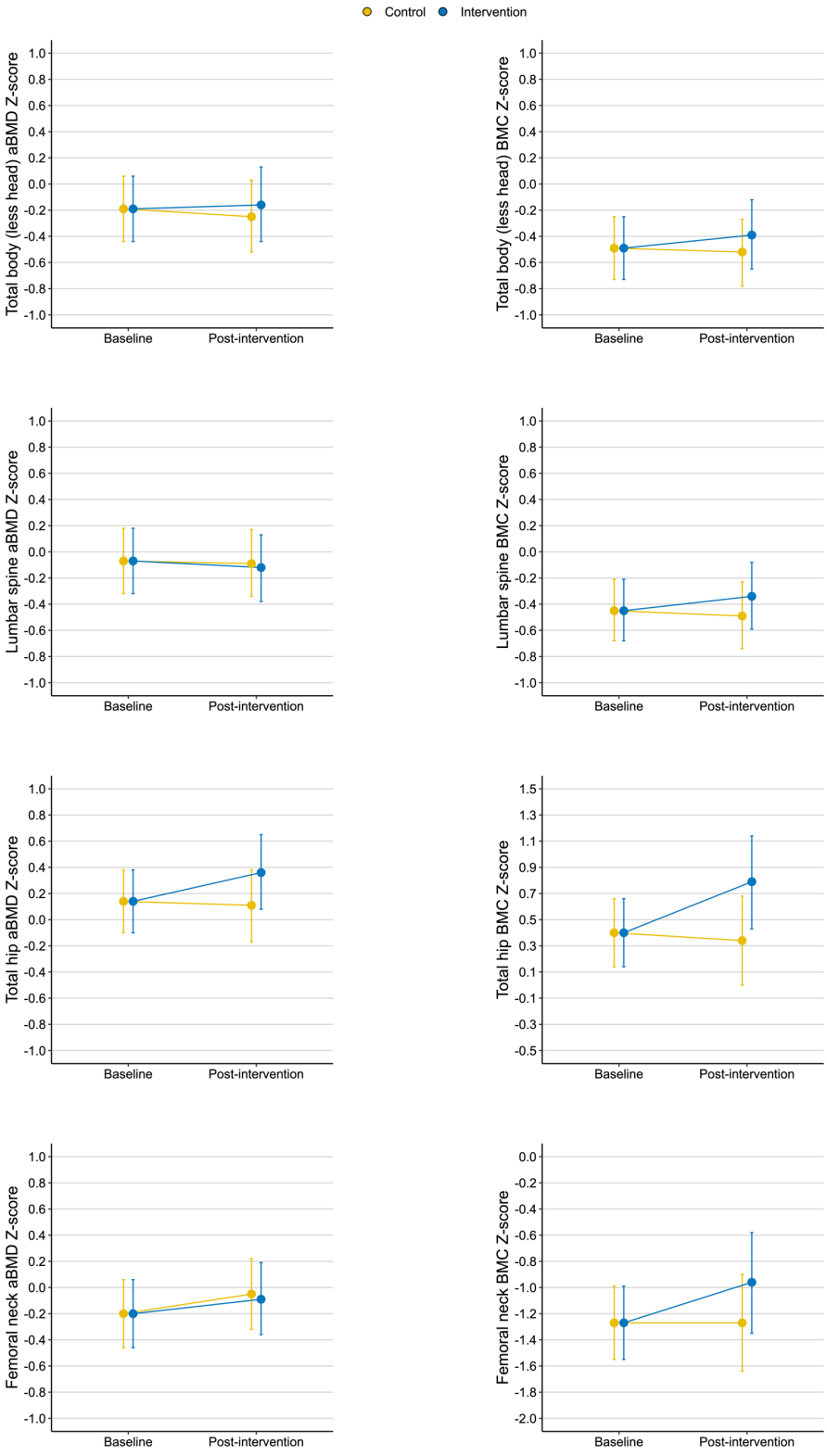

Figure 2. Estimated means at constrained baseline and 9-month post-intervention follow-up in the aBMD and BMC Z-score outcomes. Error bars represent 95% confidence intervals. Data were analyzed using a constrained baseline longitudinal mixed model adjusted for baseline differences between groups. Abbreviations: aBMD, areal bone mineral density; BMC, bone mineral content.

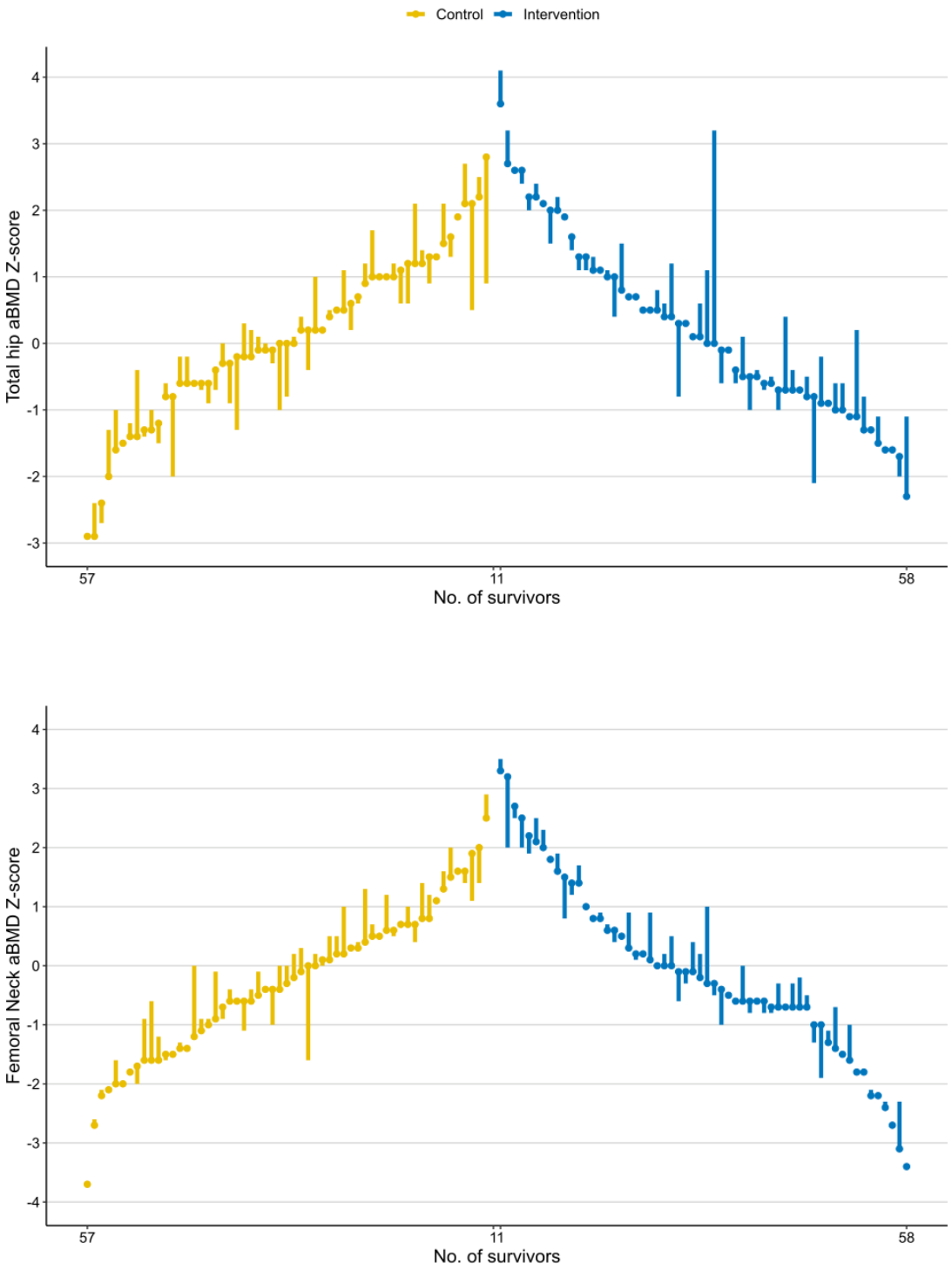

Figure 3. Parallel line plot containing one vertical line for each participant, which extends from their baseline value to their 9-month value. Ascending lines indicate an improvement in total hip and femoral neck aBMD Z-score. Baseline values are placed in ascending order for the control group and descending order for the intervention group. Abbreviations: aBMD, areal bone mineral density.

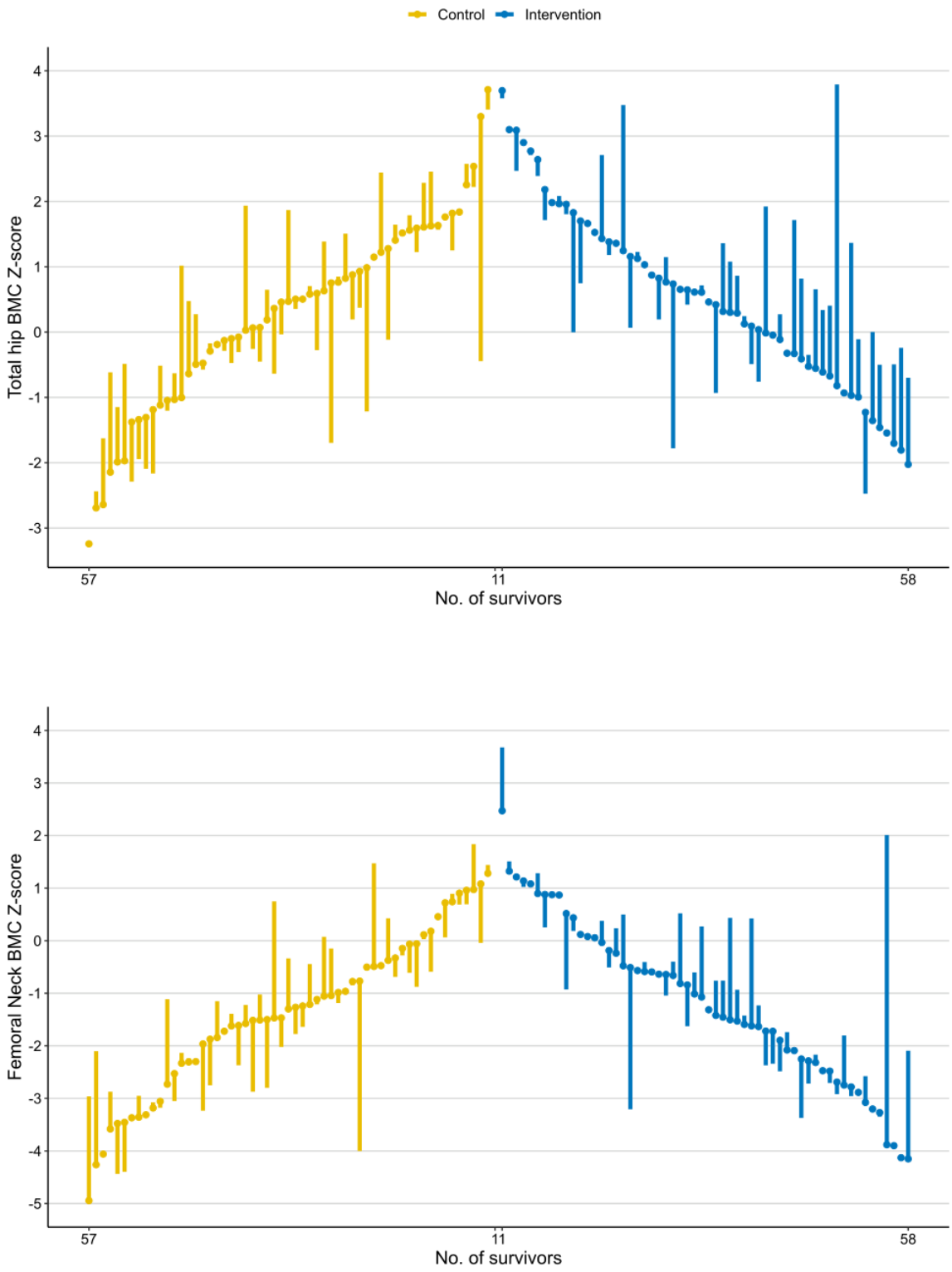

Figure 4. Parallel line plot containing one vertical line for each participant, which extends from their baseline value to their 9-month value. Ascending lines indicate an improvement in total hip and femoral neck BMC Z-score. Baseline values are placed in ascending order for the control group and descending order for the intervention group. Abbreviations: BMC, bone mineral content.

Discussion

This RCT shows that a 9-month online resistance exercise intervention of high impact loading does not significantly increase femoral neck aBMD Z-score, yet it induced improvements at the hip region in young pediatric cancer survivors. We rely mainly on the observed small-sized effects on total hip BMC Z-score using intention-to-treat analysis [32]. Of note is that those who completed at least the minimum number of the recommended exercise sessions (per-protocol analysis) showed additional significant improvements on femoral neck BMC Z-score without major, mild or minor adverse events throughout the intervention. Considering the limitations of most previous study designs and sample sizes [13-15], our RCT could provide important clinical implications regarding the causal effects of resistance exercise of high impact loading on bone health at the hip region in young pediatric cancer survivors. However, future studies are needed to confirm whether resistance exercise interventions of high impact loading, including supervised full-body exercise sessions, can improve bone health at femoral neck aBMD Z-score and other key regions in this population.

Contrary to a previous systematic review in healthy children and adolescents that reported positive effects of plyometric exercise-based interventions on femoral neck aBMD [11], our intervention was not efficacious. Yet non-supervised exercise interventions can improve bone health in adult population [33], the lack of supervision in our intervention, especially in growing population, could have affected its efficacy (i.e., intensity, motivation). However, we detected small-sized effects on total hip and femoral neck BMC Z-score (intention-to-treat and per-protocol analyses, respectively). During a sensitive period of life (i.e., childhood) for bone remodeling, these improvements could underscore important public health implications reducing the risk of osteopenia/osteoporosis [6,7], and subsequent fractures [8], reducing the odds of required hospitalization, rehabilitation, after-hospital care and future disability [4]. Although the optimal intensity, duration and volume remains unclear [11], most of the effective intervention's durations ranged from eight to 12 months which align with the duration of our intervention. From a bone perspective, this is clear since the bone remodeling process takes approximately five months and therefore, shorter interventions might not reflect true bone adaptations [34]. In addition, the use of behavior change techniques in our intervention, as recommended in long-lasting interventions in growing population [35,36], could have also helped to reach the high adherence observed. Prior investigations in young pediatric cancer survivors evaluating the effects of concurrent exercise interventions on the hip region (i.e., femoral neck aBMD, volumetric aBMD, age-, sex-, and race-specific aBMD, BMC) have not detected significant effects [14,15]. Reasons for this may include short trial duration (i.e., three months)

[14], inclusion of aerobic/non-osteogenic exercises (i.e., cycling, swimming) [15] or microgravity environments (i.e., swimming pools) [14], which were factors that we avoided in our intervention. Therefore, young pediatric cancer survivors at risk of low aBMD at the hip region could be referred to exercise-oncology plans based on resistance exercise of high impact loading to improve bone health.

Our resistance exercise intervention was not efficacious at improving bone health at total body, yet we observed small-sized effects on total body BMC Z-scores (per-protocol analysis). In healthy children and adolescents [11], the referred systematic review reported positive effects of similar interventions (i.e., plyometric exercise-based) on total body aBMD and BMC outcomes. In young pediatric cancer survivors, Mogil et al. [37] observed significant effects (P = .05) of a low-magnitude, high-frequency mechanical stimulation during one year, seven days/week and two sessions per day lasting 10 minutes each on total body aBMD Z-scores. The timing of the frequency (twice per day) and adequate intervention duration (one year) could explain these positive findings. This program is not entirely similar to our intervention due to the use of an external active platform and hence, this hampers further comparisons. Similar to our findings, a non-RCT evaluating the effects of a concurrent full-body exercise intervention during six months, three days/week and lasting 55-60 minutes each in survivors did not find significant effects on total body aBMD Z-scores [15]. Although our intervention was specifically designed to improve bone health following the training principles of previous successful interventions in healthy children and adolescents [38,39], it lacked core and upper-body exercises that might have improved muscle strength/mass that could have created the needed stimulus for bone mass to increase, according to the mechanostat theory of Frost [40]. This may also explain why we only found small-sized effects (borderline) on lumbar spine BMC Z-score (per-protocol analysis). In healthy children and adolescents, the mentioned systematic review [11], did show positive effects on lumbar spine aBMD and BMC outcomes. However, in young pediatric cancer survivors, two exercise interventions not primarily focused on improving bone [13] and non-osteogenic [14], in addition to the studies of Mogil et al. [37] and Dubnov-Raz [15], did not observe significant effects on aBMD, volumetric aBMD, age-, sex-, and race-specific aBMD, BMC at lumbar spine. Altogether, our RCT suggests that bone adaptations are site-specific since the observed effects are mainly found at the hip region, which was our main target. Nevertheless, future studies are needed to confirm whether resistance exercise interventions of high impact loading, including supervised full-body exercise sessions, can improve bone health at femoral neck aBMD Z-score and other key regions so that they can be incorporated into surveillance guidelines and provide a foundation for individualized

exercise-oncology plans development, specifically adapted to the needs of the pediatric cancer survivors.

Limitations

The interpretation of the results of this study should be made in conjunction with some limitations. First, although the adherence with the intervention was monitored using a diary that was monthly reviewed, the exercise sessions were not supervised throughout the intervention. Nevertheless, parents provided the necessary support when needed and research staff kept frequent contact via WhatsApp Groups. In fact, we observed higher positive effects when meeting the minimum of the recommended exercise sessions (per-protocol analysis) suggesting that those who reported more sessions performed obtained the greatest benefits. Second, COVID-19 restrictions did not enable this RCT to be conducted under usual settings potentially affecting intensity required and motivation. Third, pediatric cancer is a rare disease and hence, recruiting participants is challenging. Future studies, if possible, may test the benefits of a similar resistance exercise intervention in survivors with low aBMD. Fourth, even though we used a parallel-group RCT (1:1) design, we could not control for potential confounding by differences in other factors that considerably influence bone growth such as genetics. Finally, we could not determine whether bone health improvements at the hip region are sustained over time following the cessation of our intervention.

Conclusion

The findings of this RCT show that a 9-month online resistance exercise intervention of high impact loading does not increase femoral neck aBMD Z-score, yet it induces improvements at the hip region in young pediatric cancer survivors. During a sensitive period of life (i.e., childhood) for bone remodeling, these improvements may contribute to reducing the risk of osteopenia/osteoporosis and fractures at this site later in life. Future studies are needed to confirm whether supervised full-body resistance exercise interventions of high impact loading can improve bone health at femoral neck aBMD Z-score and other key regions maximizing its benefits in this population.

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Supplementary Material

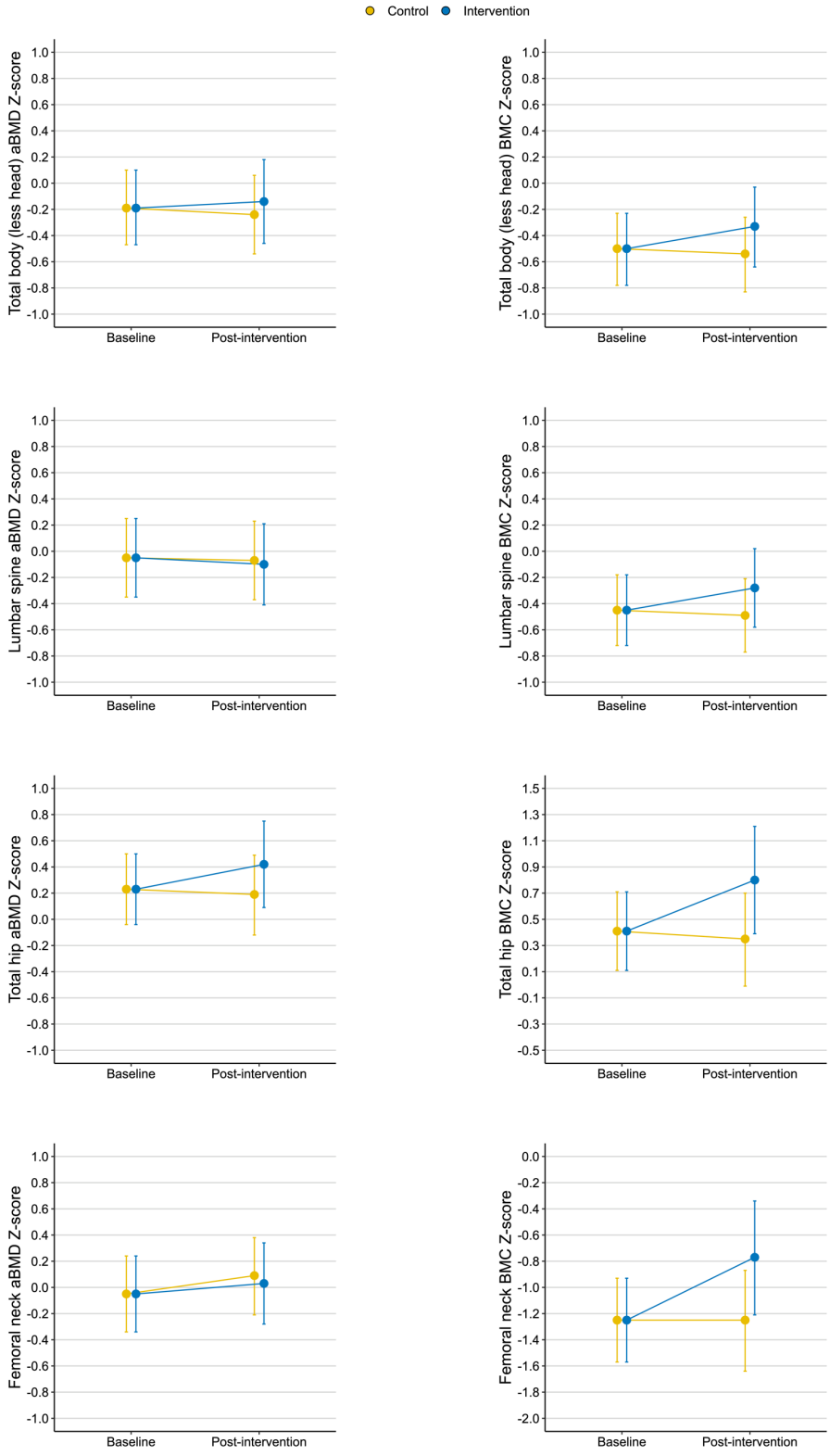

Figure S1. Estimated means at constrained baseline and 9-month post-intervention follow-up in the aBMD and BMC Z-score outcomes. Error bars represent 95% confidence intervals. Data were analyzed using a constrained baseline longitudinal mixed model adjusted for baseline differences between groups. Abbreviations: aBMD, areal bone mineral density; BMC, bone mineral content.

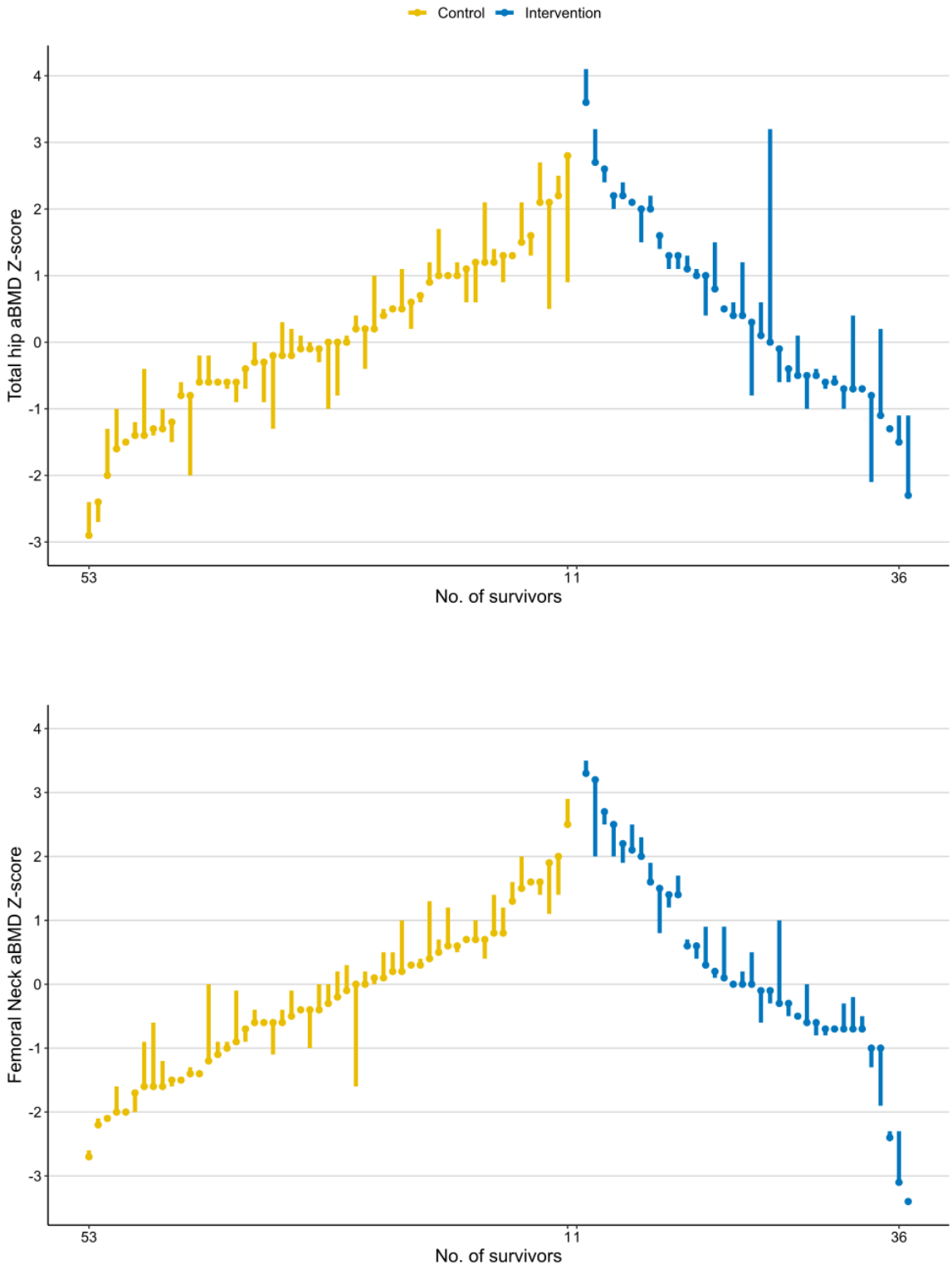

Figure S2. Parallel line plot containing one vertical line for each participant, which extends from their baseline value to their 9-month value. Ascending lines indicate an improvement in total hip and femoral neck aBMD Z-score. Baseline values are placed in ascending order for the control group and descending order for the intervention group. The individual response (51% and 49% responders, respectively) was calculated using the technical error of measurement from the control group proposed by Brennan et al. [(2)]. Abbreviations: aBMD, areal bone mineral density.

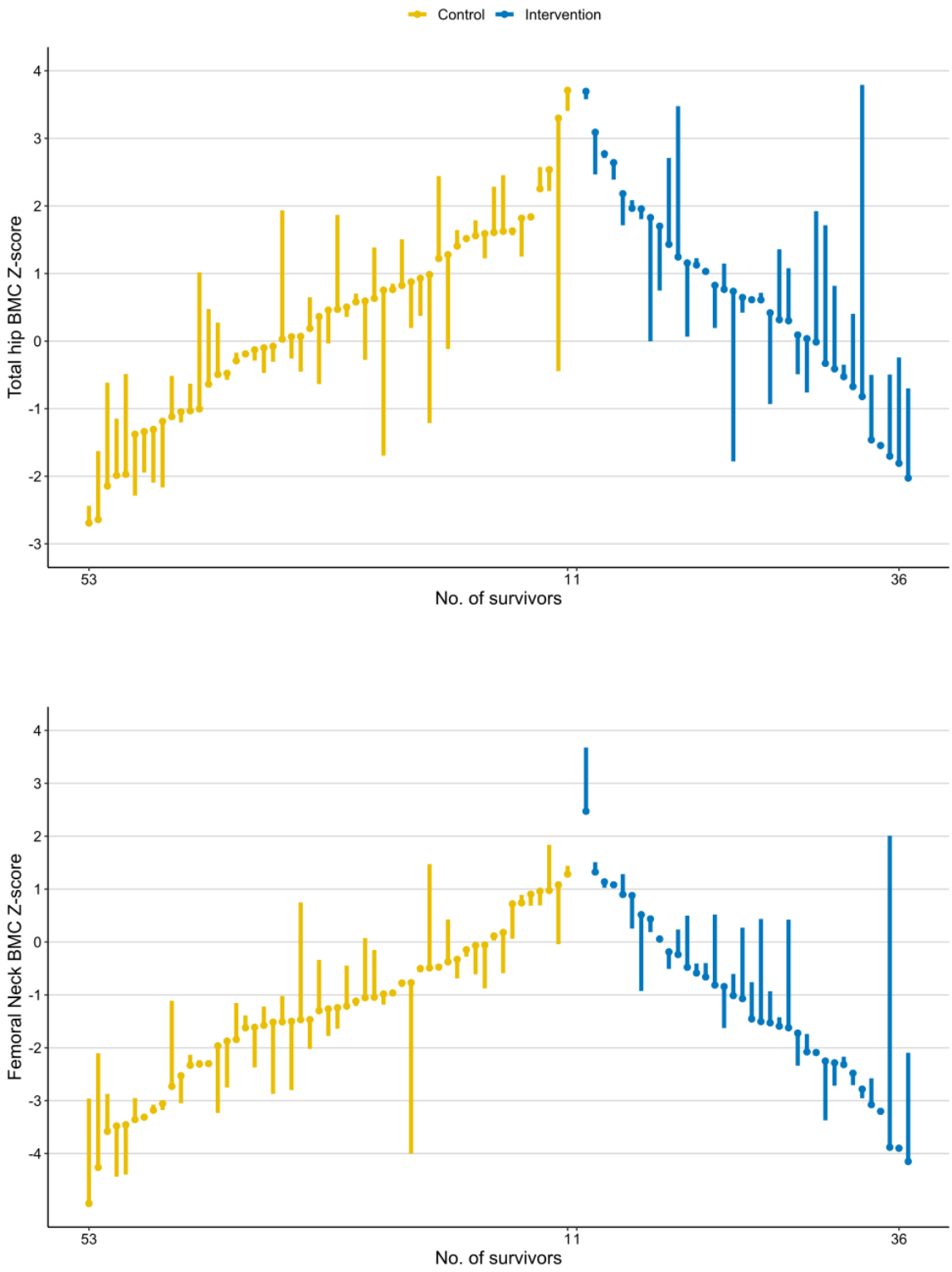

Figure S3. Parallel line plot containing one vertical line for each participant, which extends from their baseline value to their 9-month value. Ascending lines indicate an improvement in total hip and femoral neck BMC Z-score. Baseline values are placed in ascending order for the control group and descending order for the intervention group. The individual response (43% and 57% responders, respectively) was calculated using the technical error of measurement from the control group proposed by Brennan et al. [(2)]. Abbreviations: BMC, bone mineral content.

Table S1. CONSRT 2010 checklist.

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	245
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	245
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	246
	2b	Specific objectives or hypotheses	246
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	246-247
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	247
	4b	Settings and locations where the data were collected	247-249
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	247-248
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	249
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	247
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	247
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	247
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	247
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	247

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	247
	11b	If relevant, description of the similarity of interventions	247-248
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	250
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	250
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	250-251
	13b	For each group, losses and exclusions after randomisation, together with reasons	250-251
Recruitment	14a	Dates defining the periods of recruitment and follow-up	247
	14b	Why the trial ended or was stopped	247
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	251
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	255
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	254
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	259
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	261
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	261
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	259-261
Other information			
Registration	23	Registration number and name of trial registry	246-247
Protocol	24	Where the full trial protocol can be accessed, if available	246-247
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	-

Table S2. Distribution of cancer types of survivors included in this study.

	Total	N	Intervention	N	Control	N
Type of cancer (%)						
Acute lymphoblastic leukemia	38.8	45	39.7	23	37.9	22
Lymphoma	12.1	14	8.6	5	15.5	9
Central nervous system	9.5	11	10.3	6	8.6	5
Renal tumor	7.8	9	6.9	4	8.6	5
Neuroblastoma	6.9	8	8.6	5	5.2	3
Malignant bone tumor	6.9	8	6.9	4	6.9	4
Histiocytosis	5.2	6	6.9	4	3.4	2
Soft tissue and other extraosseous sarcomas	4.3	5	5.2	3	3.4	2
Retinoblastoma	3.4	4	3.4	2	3.4	2
Hepatic tumor	2.6	3	1.7	1	3.4	2
Other malignant epithelial neoplasms	1.7	2	1.7	1	3.4	2
Unknown	0.9	1	0.0	0	0.0	0

Data are presented as percentages and frequencies.

Table S3. Baseline and at nine months aBMD and BMC Z-score outcomes using intention-to-treat approach.

	Intervention	Control
	Mean (95% CI)	Mean (95% CI)
aBMD Z-score		
Femoral neck		
Baseline	-0.20 (-0.46 to 0.06)	-0.20 (-0.46 to 0.06)
9-month	-0.09 (-0.36 to 0.19)	-0.05 (-0.32 to 0.22)
Total hip		
Baseline	0.14 (-0.10 to 0.38)	0.14 (-0.10 to 0.38)
9-month	0.36 (0.08 to 0.65)	0.11 (-0.17 to 0.38)
Total body (less head)		
Baseline	-0.19 (-0.44 to 0.06)	-0.19 (-0.44 to 0.06)
9-month	-0.16 (-0.44 to 0.13)	-0.25 (-0.52 to 0.03)
Lumbar spine		
Baseline	-0.07 (-0.32 to 0.18)	-0.07 (-0.32 to 0.18)
9-month	-0.12 (-0.38 to 0.13)	-0.09 (-0.34 to 0.17)
BMC Z-score		
Femoral neck		
Baseline	-1.27 (-1.55 to -0.99)	-1.27 (-1.55 to -0.99)
9-month	-0.96 (-1.35 to -0.58)	-1.27 (-1.64 to -0.90)
Total hip		
Baseline	0.40 (0.14 to 0.66)	0.40 (0.14 to 0.66)
9-month	0.79 (0.43 to 1.14)	0.34 (0.00 to 0.68)
Total body (less head)		
Baseline	-0.49 (-0.73 to -0.25)	-0.49 (-0.73 to -0.25)
9-month	-0.39 (-0.65 to -0.12)	-0.52 (-0.78 to -0.27)
Lumbar spine		
Baseline	-0.45 (-0.68 to -0.21)	-0.45 (-0.68 to -0.21)
9-month	-0.34 (-0.59 to -0.08)	-0.49 (-0.74 to -0.23)

Results are presented as mean (95% CI) at baseline and 9-month post-intervention follow-up for each group. Data were analyzed using a constrained baseline longitudinal mixed model adjusted for baseline differences between groups. Age-, sex-, and race-specific aBMD and BMC Z-scores at each site are presented using international reference data from the Bone Mineral Density in Childhood Study [(1)]. Abbreviations: aBMD, areal bone mineral density; BMC, bone mineral content; CI, confidence interval.

Table S4. Within-group changes (baseline to nine months) and between-group differences (intervention vs. control) in the aBMD and BMC Z-score outcomes.

	Intervention		Control		Between-group Differences		
	Change (95% CI)	Change %[Ψ]	Change (95% CI)	Change %[Ψ]	MD (95% CI)	Effect size	*P*[†]
aBMD Z-score							
Femoral neck	0.08 (-0.11 to 0.28)	2.70	0.14 (-0.02 to 0.30)	4.05	-0.06 (-0.27 to 0.15)	-0.12	.598
Total hip	0.20 (-0.08 to 0.47)	4.82	-0.04 (-0.27 to 0.18)	-2.41	0.24 (-0.06 to 0.53)	0.35	.111
Total body (less head)	0.05 (-0.18 to 0.27)	3.80	-0.06 (-0.24 to 0.13)	-3.80	0.10 (-0.14 to 0.35)	0.19	.409
Lumbar spine	-0.05 (-0.20 to 0.10)	-2.70	-0.02 (-0.14 to 0.10)	-2.70	-0.03 (-0.19 to 0.13)	-0.08	.704
BMC Z-score							
Femoral neck	0.47 (0.04 to 0.91)	13.09	0.00 (-0.36 to 0.36)	7.27	0.48 (0.02 to 0.94)	0.43	**.043**
Total hip	0.39 (-0.06 to 0.84)	13.17	-0.06 (-0.44 to 0.31)	-8.70	0.45 (-0.01 to 0.92)	0.39	.057
Total body (less head)	0.17 (-0.03 to 0.37)	8.59	-0.04 (-0.20 to 0.13)	-7.05	0.21 (-0.01 to 0.42)	0.42	.058
Lumbar spine	0.17 (-0.02 to 0.37)	9.02	-0.04 (-0.20 to 0.12)	-7.00	0.21 (0.00 to 0.42)	0.42	.050

Results are presented as mean change from baseline for each group and as mean difference between groups change. Data were analyzed using a constrained baseline longitudinal mixed model adjusted for baseline differences between groups. Age-, sex-, and race-specific aBMD and BMC Z-scores at each site are presented using international reference data from the Bone Mineral Density in Childhood Study [(1)]. Effect sizes were calculated following Cohen's d formula. Abbreviations: aBMD, areal bone mineral density; BMC, bone mineral content; MD, mean difference.

[Ψ] Change percentage was calculated from raw values (g/cm^2 or g).

[†] P-values showed between-group differences on the aBMD and BMC Z-score outcomes.

Table S5. Baseline and at nine months aBMD and BMC Z-score outcomes using per-protocol approach.

	Intervention	Control
	Mean (95% CI)	Mean (95% CI)
aBMD Z-score		
Femoral neck		
Baseline	-0.05 (-0.34 to 0.24)	-0.05 (-0.34 to 0.24)
9-month	0.03 (-0.28 to 0.34)	0.09 (-0.21 to 0.38)
Total hip		
Baseline	0.23 (-0.04 to 0.50)	0.23 (-0.04 to 0.50)
9-month	0.42 (0.09 to 0.75)	0.19 (-0.12 to 0.49)
Total body (less head)		
Baseline	-0.19 (-0.47 to 0.10)	-0.19 (-0.47 to 0.10)
9-month	-0.14 (-0.46 to 0.18)	-0.24 (-0.54 to 0.06)
Lumbar spine		
Baseline	-0.05 (-0.35 to 0.25)	-0.05 (-0.35 to 0.25)
9-month	-0.10 (-0.41 to 0.21)	-0.07 (-0.37 to 0.23)
BMC Z-score		
Femoral neck		
Baseline	-1.25 (-1.57 to -0.93)	-1.25 (-1.57 to -0.93)
9-month	-0.77 (-1.21 to -0.34)	-1.25 (-1.64 to -0.87)
Total hip		
Baseline	0.41 (0.11 to 0.71)	0.41 (0.11 to 0.71)
9-month	0.80 (0.39 to 1.21)	0.35 (-0.01 to 0.70)
Total body (less head)		
Baseline	-0.50 (-0.78 to -0.23)	-0.50 (-0.78 to -0.23)
9-month	-0.33 (-0.64 to -0.03)	-0.54 (-0.83 to -0.26)
Lumbar spine		
Baseline	-0.45 (-0.72 to -0.18)	-0.45 (-0.72 to -0.18)
9-month	-0.28 (-0.58 to 0.02)	-0.49 (-0.77 to -0.21)

Results are presented as mean (95% CI) at baseline and 9-month post-intervention follow-up for each group. Data were analyzed using a constrained baseline longitudinal mixed model adjusted for baseline differences between groups. Age-, sex-, and race-specific aBMD and BMC Z-scores at each site are presented using international reference data from the Bone Mineral Density in Childhood Study [(1)]. Abbreviations: aBMD, areal bone mineral density; BMC, bone mineral content; CI, confidence interval.

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GENERAL DISCUSSION

Chapter 11. An integrative discussion of the International Doctoral Thesis

General discussion

Pediatric cancer is one of the main causes of mortality during childhood and adolescence, and its incidence has considerably increased over the last decades [1]. Intensive anticancer therapies received at very young ages interfere with normal growth and skeletal development [2-4] leading to low aBMD identified in up to two-thirds of pediatric cancer survivors [5]. Therefore, identifying effective strategies to counteract bone loss in this population is needed to reduce the increased risk of osteopenia/osteoporosis in adulthood [6,7], which may well lead to higher risk of fractures later in life [8]. Non-pharmacological interventions, such as exercise, are well-known to successfully improve aBMD in healthy children and hence, a similar osteogenic effect could be observed in young pediatric cancer survivors [9]. Resistance exercise of high impact loading contributes to bone accrual during growth mass since the impacts produced against the ground of this exercise type causes higher forces on the bones and the needed stimulus for their development [10]. Thus, the initial objective of this International Doctoral Thesis was to investigate whether previous exercise interventions are effective at improving bone health in children and adolescents with cancer during and after oncological treatment (**Chapter 4**).

During oncological treatment, there is no evidence of beneficial effects of exercise on bone parameters in children and adolescents. First and foremost, one of the most common side effects during oncological treatment is cancer-related fatigue [11,12]. This may be reflected by the poor adherence of participants to the exercise interventions as in the study of Hartman et al. [13], in which 36% of participants exercised less than once a week. This could have been an important barrier to achieve the required exercise intensity to effectively stimulate the bone and to obtain bone adaptations. Secondly, the prescribed exercise type might not have been appropriate to obtain bone adaptations in some studies. Although resistance exercise of high impact loading significantly contribute bone development, this type of exercise was not chosen in the studies of Müller et al. [14] and Waked [15], and when included, the intensity required to modify bone parameters was not achievable as mentioned in the study of Cox et al. [16]. The latter intervention was proven not to be feasible during the early oncological treatment phase owing to the children's responses to the disease and the treatment.

Shortly after oncological treatment, there is no evidence of positive effects of exercise interventions aimed at improving bone parameters. One of the potential factors could be the

short duration as half of the interventions lasted for only three months [17,18]. The bone remodeling process takes approximately 5 months and therefore, shorter interventions could not reflect true bone adaptations [19]. In addition, the type of exercise was not the most appropriate to improve bone parameters in some cases. Dubnov-Raz et al. [20] did not include resistance exercise of high impact loading, yet participants reported to be mentally and physically healthier than those in previous studies during oncological treatment [16]. Likewise, Elnaggar et al. [17] included lower-body plyometric exercises in a swimming pool, that is, in a microgravity environment, which is not effective at increasing bone parameters [21]. Nevertheless, Mogil et al. [22] implemented an intervention including standing on an active vibration platform emitting low-magnitude high-frequency mechanical stimulation, considered a type of high impact loading physical activity as it requires muscles and bones to work against gravity [23,24]. From the included studies, the latter was the only intervention that observed a borderline significant increase in total body aBMD. The timing of the intervention (i.e., after oncological treatment), the frequency (twice per day) and adequate intervention duration (one year) could explain the findings. However, this intervention type was ineffective at increasing lumbar spine aBMD outcomes. As stated by the authors, this might have been caused by the potential loss of vibratory energy as the signal travelled from the distal lower extremity to the trunk. This agreed with a recent systematic review and meta-analysis in children and adolescents with motor disabilities that found no pooled effect of similar interventions on lumbar spine aBMD [25].

Our systematic review and meta-analysis indicate that previous exercise interventions have not been specifically designed to improve bone health and therefore, they have been ineffective to illustrate any beneficial effect on bone of children and adolescents with cancer during and after oncological treatment. Several limitations in the design of the interventions have been identified. Considering these findings and the fact that the pathogenesis of the accelerated aBMD decline in pediatric cancer survivors is multifactorial [26], avoiding an abnormal body composition, unhealthy lifestyle and physical fitness deficits could be linked to enhanced bone health (**Chapters 5-9**). Therefore, we firstly aimed to examine the contribution of independent predictors to bone parameters in young pediatric cancer survivors (**Chapter 5**).

The findings of this cross-sectional study shows that the strongest positive determinant is region-specific lean mass which is consistent with findings from previous studies in healthy children and adolescents [27] and, children with cancer during [28] and after oncological treatment [29,30]. This could be explained mainly due to the Frost's mechanostat theory since inadequate lean mass acquisition impairs bone development [31]. In relation to the association

of region-specific fat mass and aBMD parameters, our findings indicate negligible associations after accounting for other predictors in the model. The strong effect of other predictors such as years from PHV and sex are likely to moderate the relationship between fat mass and bone parameters [32]. However, contrary findings were found by Mostoufi-Moab et al. [33] in survivors of pediatric hematopoietic stem cell transplantation (aged 12-25 years). In their study, fat mass was inversely associated with abnormal trabecular architecture. Discrepancies between studies might be explained by the differences in the age of the participants, number of predictor variables as well as the pediatric cancer treatment received by the participants since both hematopoietic stem cell transplantation and total body irradiation are known to impair the normal fat-bone axis [34]. We also found that years from PHV have a positive association with aBMD at total body less head, legs and arms aBMD. In this regard, pre, peri and postpubertal periods are vital periods for bone development during normal growth [35] and even more critical after pediatric cancer diagnosis [29]. Time from treatment completion also has a positive association with femoral neck and total hip aBMD. This backs up that aBMD parameters improve with increasing time-off therapy after the exposure to oncological treatment [26].

Previous studies in healthy population showed that HSA can provide more thorough geometrical evaluation at the hip site compared with aBMD parameters [36]. In agreement with Macdonald et al. [37], the results of our study highlight the association of region-specific lean mass and HSA parameters during childhood and adolescence. Prior reports in allogeneic hematopoietic stem cell transplantation survivors showed alterations in body composition following oncological treatment; increased fat mass while lean mass did the opposite [38]. These alterations partially explained the substantial deficits in trabecular volumetric bone mineral density and cortical geometry [39]. We did not find that region-specific fat mass is associated with any HSA parameters. However, the differences in the population characteristics, evaluation techniques and the region of interest make the studies incomparable. Of note, Mostoufi-Moab et al. [39] assessed bone, lean and fat mass at the 66% site of tibia using peripheral quantitative computed tomography. In our study, the time-off therapy is positively associated with the narrow neck cross sectional area after the exposure to oncological treatment like the femoral neck aBMD. This is consistent with findings of a previous review which identified that following completion of oncological therapy there is a substantial recovery in the femoral neck geometrical property [40]. Similar to aBMD and HSA parameters, the strongest determinant for the TBS is region-specific lean mass which agrees with previous studies in healthy population [41]. However, they did not distinguish the site-specific relationship of lean mass which, in fact, is considered in the present study. Female sex in this cohort has a positive

association with bone texture acquisition at the lumbar spine, showing a diminished contribution once other factors (i.e., region-specific lean mass) are accounted. This aligns with a previous study in which TBS at baseline was significantly higher in females than males [41]. This shows the beneficial effects of time-off therapy on bone impairments caused by oncological treatment. However, the limited number of studies using TBS in young pediatric cancer survivors does not allow further comparisons.

The results of this study suggest that lean mass is the most important determinant of most bone parameters. This underlines the clinical importance of preserving or attenuating the decline of lean mass after treatment completion [42], which could reduce the subsequent increased risk of osteopenia and/or osteoporosis during adulthood [6,7]. On the contrary, SB could increase the elevated risk of comorbidities, including low aBMD during childhood and adolescence [43]. TV watching is one of these SB highly prevalent among survivors [44] and therefore, its relationship with bone health could presumably be negative. It also remains unknown whether lean mass could have a protective role in the negative associations of TV watching time with bone parameters among young pediatric cancer survivors. Thus, our next objective was to investigate the role of lean mass in the association of TV watching time with bone parameters, and to examine whether having high lean mass attenuates the negative association of watching TV more than one hour per day with bone parameters Z-score (**Chapter 6**).

Our observational study indicates that TV watching time is negatively associated with most bone parameters in peri/post-pubertal survivors, but this association is dependent on lean mass. Importantly, those survivors watching TV more than one hour per day and with high lean mass present higher bone parameters Z-score than those with low lean mass. These findings highlight the importance of promoting musculoskeletal development while reducing TV watching time to maximize bone regeneration after pediatric cancer. The reasons why SB may limit aBMD during growth rely on the lack of mechanical forces as described by the Frost's mechanostat theory [45], which are key in the bone formation-resorption cellular activity a phenomenon previously. Prolonged TV watching time sitting or lying may reduce bone mass by augmenting bone resorption, without concomitant changes in bone formation [46]. In comparison with other sedentary activities, watching TV is characterized by spending a lot of time in the same position. As a result, prolonged time and situations without mechanical loading are likely to be detrimental for bone health [46].

The associations of TV watching time with bone parameters are found only in peri-post/pubertal pediatric cancer survivors in this study. This could be explained because peri-

post/pubertal survivors are likely to have been exposed to this behavior for a longer time [46]. This is in line with previous work in children and adolescents during and following oncological treatment that showed less capacity to recover from fractures in the older ones due to insufficient residual growth potential [47]. Previous research in pediatric cancer survivors aged nine to 18 years old showed a higher risk of having reduced whole body aBMD in those watching TV more than two hours per day, after controlling for sex, age, ethnicity and pubertal stage (mean pubertal stage around their PHV) [48]. Likewise, Gunes et al. [49], indicated that TV watching time was negatively associated with aBMD at lumbar spine (L2-L4) in children completing treatment for acute lymphoblastic leukemia. However, their analyses were not controlled for any covariates such as lean mass nor somatic maturity despite the importance of lean mass [47], and the survivors' age range (3.4 to 17.5 years old). In contrast, Kelly et al. [50] did not find significant associations of TV watching time with whole body aBMD (including head) after controlling for age, ethnicity, height, weight and total body bone area in children with acute lymphoblastic leukemia during and following completion of treatment (aged 3 to 18 years old). In this study, most significant associations of TV watching time with bone parameters attenuated to the null once region-specific lean mass was controlled in the models [51]. Surprisingly, none of the previous-mentioned studies accounted for lean mass despite being one of the strongest predictors of bone parameters during growth [47], which hampers comparisons in this regard [51]. Additionally, those with high lean mass present significantly higher bone parameters Z-score than survivors with low lean mass (among those watching TV more than one hour per day). In line with the study of Polgreen et al. [48], these findings show the protective role of lean mass for bone health when a prolonged SB such as TV watching time is prevalent.

The international physical activity guidelines for pediatric cancer survivors underline the importance of not only limiting SB, but also engaging in at least an average of 60 min of MVPA per day [52,53]. However, only one-third of survivors meet these recommendations even years after pediatric cancer diagnosis (7.0 $\pm$ 3.3 years) [54]. This modifiable lifestyle factor can contribute to bone development [55]. Self-reported physical activity has been associated with higher total body aBMD [56], and lumbar spine aBMD Z-score [48,56,57] in survivors. Nevertheless, previous studies using both objective and self-reported methods did not show robust associations of SB with lower total body and lumbar spine aBMD Z-score [48,49,50]. Likewise, research in children and adolescents does not consistently show associations of sleep with aBMD parameters [58] while short sleep has been reported in almost half of 911 adult pediatric cancer survivors [59]. The existing literature regarding the associations of physical

activity, SB and sleep with bone health in young pediatric cancer survivors is limited by important knowledge gaps including self-reported measures, small sample sizes and methodological shortcomings. Therefore, we aimed to examine the associations of 24-hour movement behaviors (MVPA, LPA, SB, and sleep) with age-, sex- and race-specific aBMD parameters at clinical sites in pre-pubertal and peri/post-pubertal cancer survivors using compositional data analysis (**Chapter 7**).

The predicted associations of MVPA with higher aBMD are significant at most sites in pre-pubertal young pediatric cancer survivors. In peri/post-pubertal survivors with low MVPA levels (21.2 min/day), LPA is significantly associated with higher aBMD at all sites. Additionally, replacing MVPA or LPA with SB is significantly associated with lower aBMD at most sites in pre-pubertal and peri/post-pubertal survivors, respectively. In healthy children aged two to five years, Taylor et al. [60] also found that increasing MVPA, while proportionally reducing LPA, SB and sleep was significantly associated with higher total body aBMD using compositional data analysis, partially similar to our findings. Likewise, using self-reported methods, one study showed significant correlations between physical activity levels and higher total body aBMD Z-score in pediatric cancer survivors [56], which is partially in line with our results. However, authors did not account for somatic maturity differences, even though survivors' age range was remarkably wide (4-32 years). On the contrary, Kadan-Lottick et al. [61] and Polgreen et al. [48] did not find similar findings. Some of the reasons that might explain why our results differ are that somatic maturity differences (49% survivors were pre-pubertal) were not considered by Kadan-Lottick et al. [61] and the different physical activity levels and/or intensities were not accounted by Polgreen et al. [48].

Concerning total hip and femoral neck aBMD, Bordbar et al. [62] showed that physical activity levels were not significantly associated with femoral neck aBMD Z-score in acute lymphoblastic leukemia survivors (mostly pre-pubertal), which agrees with our findings. Similarly, in young adult pediatric cancer survivors, two studies [63,64] did not find significant associations of physical activity levels with total hip nor femoral neck aBMD Z-score, which is in partial agreement with our findings since these survivors' somatic maturity was greater than that of our peri/post pubertal group. Regarding lumbar spine aBMD, previous reports have shown that physical activity levels were significantly associated with higher lumbar spine aBMD Z-score [48,56,57]. However, these findings did not fully agree with ours since the included survivors in these studies were mostly peri/post-pubertal. Altogether, the reason why we do not find MVPA to be significantly associated with higher aBMD in our peri/post-pubertal survivors might be due to their low levels (21.2 min/day). For this reason, when the time spent in MVPA

is around the recommended levels such as in our pre-pubertal survivors, most reallocations show significant positive effects on aBMD parameters, which is in line with previous records [9,65]. In healthy children and adolescents with different somatic maturity groups, physical activity interventions have provided evidence of the remarkable responsiveness of bone cells during the pre-pubertal stage [66,67].

All previous-mentioned studies in young pediatric cancer survivors did not distinguish physical activity intensities and hence, this hampers further comparisons with our findings increasing LPA. Previous reports in healthy children and adolescents have demonstrated the high impact of MVPA on aBMD parameters [9,65]. However, when low MVPA levels were present, increasing LPA while proportionally reducing MVPA, SB and sleep has been significantly associated with higher total body aBMD using compositional data analysis [60]. Moreover, LPA has been shown to decelerate age-related bone loss in older adults [68]. These positive findings of LPA align with our results in peri/post-pubertal survivors who also have low MVPA levels (21.2 min/day). For this reason, when low MVPA levels are not present, replacing MVPA with LPA does not illustrate a significant positive effect on aBMD at any sites in pre-pubertal survivors. Moreover, the replacement of SB or sleep with LPA in peri/post-pubertal survivors shows a significant positive effect on aBMD at most sites.

Reallocating time to SB from MVPA, LPA and sleep was not significantly associated with total body aBMD in healthy children aged from two to five years using compositional data analysis [60]. Using self-reported methods, two studies [48,49] including pre-pubertal and peri/post-pubertal survivors together reported that screen time were significantly associated with lower total body and lumbar spine aBMD Z-score which partially agrees with our findings. Conversely, Kelly et al. [50] reported that screen time was not significantly associated with total body aBMD Z-score, but the age range of the included survivors was quite wide (3-19 years), and authors did not account for somatic maturity differences. Therefore, analyses divided by somatic maturity groups could have shown different results. Our findings show the significant negative effect of SB on aBMD at most sites when replacing MVPA or LPA with SB in pre-pubertal and peri/post-pubertal survivors, respectively. Increasing sleep, while proportionally reducing MVPA, LPA and SB is negatively associated with total body aBMD in healthy children aged five years old using compositional data analysis [60]. Likewise, we found significant associations with reduced aBMD at total body and total hip when increasing sleep. In healthy children and adolescent, there seems to be an optimal duration of sleep, beyond which its beneficial associations with aBMD parameters may decline [69]. This might explain our findings because excessive sleep leaves less time available for MVPA and LPA and

therefore, the absence of mechanical strains elicited by physical activity could possibly affect bone development [70].

The findings of this study show that every move counts and underline the benefits of increasing MVPA or LPA to maximize bone regeneration following pediatric cancer treatment completion, reinforcing the international physical activity guidelines for pediatric cancer survivors [52,53]. Similarly, the engagement in regular physical activity, and the subsequent improvement of physical fitness (i.e., muscle strength) could also be associated with better bone health in young pediatric cancer survivors, following prior investigations in healthy population during adolescence [71] and later in life [72]. In healthy children and adolescents, measured upper- and lower-body muscle strength have been consistently associated with total body [73,74], upper [71,75] and lower [71,75] extremities BMC, and total body and femoral neck aBMD [76]. Likewise, in adult pediatric cancer survivors, Joyce et al. [77] found that upper- and lower-body muscle strength was positively associated with higher aBMD. However, in younger survivors, the literature describing associations of muscle strength with aBMD is scarce. Therefore, our next objective was to investigate the prevalence of upper- and lower-body muscle strength deficits in young pediatric cancer survivors compared to age- and sex-specific international reference data and to examine the associations of upper- and lower-body muscle strength with age-, sex- and race-specific aBMD Z-score at the total body, total hip, femoral neck and lumbar spine (**Chapter 8**).

More than half of young pediatric cancer survivors have upper- and lower-body muscle strength deficits when compared to geographically diverse updated age- and sex-specific reference values [78]. Importantly, we found that muscle strength deficits are consistently associated with lower aBMD Z-score at the total body, total hip, femoral neck and lumbar spine [79]. Each one-decile lower in muscle strength is associated with higher odds of having low aBMD Z-score by 30%-95%. Our findings of the associations of upper-body muscle strength with aBMD at multiple sites are consistent with data from reports among healthy children and adolescents. Vicente-Rodriguez et al. [73] reported that upper-body muscle strength was consistently the strongest fitness variable which positively correlated with total body BMC in 278 adolescents (13.0 to 18.5 years old); Gracia-Marco et al. [71] showed that among 234 non-active adolescents (14.8 ± 1.2 years old), those with reduced upper-body muscle strength had also lower BMC at total body and upper extremities; Saint-Maurice et al. [74] reported positive associations between upper-body muscle strength and height-adjusted total BMC in 433 children and adolescents (14.1 ± 2.3 years old); and Wang et al. [75] reported positive

correlations between maximal voluntary contraction of the elbow flexors and upper extremity BMC among 258 pubertal girls (11.2, 9.8 to 12.6 years old).

Our findings of the associations of lower-body muscle strength with aBMD are not consistent with previous findings in healthy young population since lower-body lean mass seems to be a better predictor of aBMD than muscle strength [80]. This could be because the lower extremities are subject to higher mechanical loadings than the upper extremities, with more opportunity for bone regeneration and formation [81], or because our measure of lower-body strength required not only strength, but also balance and coordination. Nevertheless, our lower-body muscle strength and aBMD results are consistent with results in non-cancer populations. Baptista et al. [76] evaluated 114 healthy younger children (8.5 ± 0.4 years old), and found positive associations between lower-body muscle strength (vertical jump test) and height-adjusted total body and femoral neck aBMD; Gracia-Marco et al. [71] evaluated non-active adolescents, and found that those with reduced lower-body muscle strength (standing long jump test) presented decreased BMC at total body and lower extremities; and Wang et al. [75] evaluated pubertal girls (11.2, 9.8 to 12.6 years old), and found that maximal isometric voluntary extension of the left knee was positively correlated with lower extremity BMC.

Considering these findings and lean mass as a key contributor to bone development, we examined whether those young pediatric cancer survivors with low lean mass, in addition to muscle strength deficits (hereafter referred to as sarcopenia), would have higher risk of low aBMD. A previous study identified that adults with sarcopenia had a four-fold higher risk of having osteoporosis compared with non-sarcopenic individuals [82]. In adult pediatric cancer survivors, sarcopenia, pre-frailty and frailty (including low aBMD) have been shown to coexist at a mean age of 33 years [83]. However, the literature depicting the associations of sarcopenia and low aBMD in younger survivors is still limited. Therefore, we aimed to evaluate aBMD differences according to sarcopenia status and to examine the risk of low aBMD Z-score in young pediatric cancer survivors with sarcopenia confirmed/probable (**Chapter 9**).

Over one-third of young pediatric cancer survivors enrolled on this study present sarcopenia confirmed and have significantly lower aBMD Z-score than survivors with no sarcopenia or sarcopenia probable at all regions. Survivors with sarcopenia confirmed have higher risk of low aBMD Z-score at total body, total hip and femoral neck, than those without sarcopenia. Previous reports [84-87] describing sarcopenia in young pediatric cancer survivors have not included functional outcomes. In our study, handgrip muscle strength in addition to ALMI via DXA were measured following the criteria of the sarcopenia definition stated by the EWGSOP2 [88]. The importance of including functional outcomes in the definition of

sarcopenia is supported by our findings as not all survivors in our study with low ALMI had muscle strength deficits. Moreover, aBMD is not impaired at any site in survivors with low ALMI, but with normal muscle strength.

Prior investigations have observed that muscle strength deficits are associated with low aBMD in pediatric cancer survivors [75], but very few have investigated whether having low ALMI in addition to muscle strength deficits (sarcopenia confirmed) would be associated with low aBMD even shortly after treatment completion. A study led by Guo et al. [89] examined the link between sarcopenia status (measuring both lean mass and ankle dorsiflexion strength) and aBMD in 20 pediatric high-risk neuroblastoma survivors (12.4 $\pm$ 1.6 years). In their study, survivors presented sarcopenia but not low aBMD after a median of nine years from diagnosis (median of 2.8 years old at diagnosis). Their sample size was small and limited to high-risk neuroblastoma survivors, whose treatment exposures likely differ from the exposures in our study population. Our results of coexisting geriatric symptoms are similar to a cohort study of 2,003 adult survivors of pediatric cancer that reported the coexistence of sarcopenia, pre-frailty and frailty (including low aBMD) at a mean age of 33 years [83].

A myriad of studies has shown that young pediatric cancer survivors are at higher risk of muscle strength deficits, low lean mass and low aBMD [5,42]. However, the interconnectedness between these premature complications have not been described together shortly after treatment completion. Given that screening for both age- and sex-specific muscle strength deficits and low lean mass is clinically recommended, our study adds to the current literature that those with impairments should be referred not only for improving muscular weakness, but also to prevent further decline in bone mass. Since sarcopenia and low aBMD are prevalent in adult pediatric cancer survivors [83], early sarcopenia identification and referral for rehabilitation are fundamental. Further research is still needed to confirm these findings in larger cohort studies so that they could be included in surveillance guidelines. Resistance training-based interventions designed to target osteosarcopenia could prevent frailty and reduce the risk for fractures later in life.

After investigating the cross-sectional relationship between SB, physical activity, lean mass and muscle function with bone health (**Chapters 5-9**), and considering the preliminary nature of previous exercise interventions evaluating bone health and the limitations associated with the study designs and sample sizes of most studies [17,18,20,22], we concluded that conducting a RCT was needed to gain a deeper understanding of the effects of a 9-month resistance exercise intervention of high impact loading on bone health in young pediatric cancer survivors

(**Chapter 10**). The design of this intervention was based on prior effective exercise interventions in healthy young population [9].

This RCT shows that a 9-month online resistance exercise intervention of high impact loading does not significantly increase femoral neck aBMD Z-score, yet it induces improvements at the hip region in young pediatric cancer survivors. We rely mainly on the observed small-sized effects on total hip BMC Z-score using intention-to-treat analysis [90]. Of note is that those who completed at least the minimum number of the recommended exercise sessions (per-protocol analysis) show additional significant improvements on femoral neck BMC Z-score without major, mild or minor adverse events throughout the intervention. Considering the limitations of most previous study designs and sample sizes [17,18,20], our RCT could provide important clinical implications regarding the causal effects of resistance exercise of high impact loading on bone health at the hip region in young pediatric cancer survivors. However, future studies are needed to confirm whether resistance exercise interventions of high impact loading, including supervised full-body exercise sessions, can improve bone health at femoral neck and other key regions in this population.

Contrary to a previous systematic review in healthy children and adolescents that reported positive effects of plyometric exercise-based interventions on femoral neck aBMD [9], our intervention is not efficacious. Yet non-supervised exercise interventions can improve bone health in adult population [91], the lack of supervision in our intervention, especially in growing population, could have affected its efficacy (i.e., intensity, motivation). However, we detect small-sized effects on total hip and femoral neck BMC Z-score (intention-to-treat and per-protocol analyses, respectively). During a sensitive period of life (i.e., childhood) for bone remodeling, these improvements could underscore important public health implications reducing the risk of osteopenia/osteoporosis [6,7], and subsequent fractures [8], reducing the odds of required hospitalization, rehabilitation, after-hospital care and future disability [26]. Although the optimal intensity, duration and volume remains unclear [9], most of the effective intervention's durations ranged from eight to 12 months which align with the duration of our intervention. From a bone perspective, this is clear since the bone remodeling process takes approximately five months and therefore, shorter interventions might not reflect true bone adaptations [19]. In addition, the use of behavior change techniques in our intervention, as recommended in long-lasting interventions in growing population [92,93], could have also helped to reach the high adherence observed. Prior investigations in young pediatric cancer survivors evaluating the effects of concurrent exercise interventions on the hip region (i.e., femoral neck aBMD, volumetric aBMD, age-, sex-, and race-specific aBMD, BMC) have not detected

significant effects [17,20]. Reasons for this may include short trial duration (i.e., three months) [17], inclusion of aerobic/non-osteogenic exercises (i.e., cycling, swimming) [20] or microgravity environments (i.e., swimming pools) [17], which were factors that we avoided in our intervention. Therefore, young pediatric cancer survivors at risk of low aBMD at the hip region could be referred to exercise-oncology plans based on resistance exercise of high impact loading to improve bone health.

Our resistance exercise intervention is not efficacious at improving bone health at total body, yet we observe small-sized effects on total body BMC Z-scores (per-protocol analysis). In healthy children and adolescents [9], the referred systematic review reported positive effects of similar interventions (i.e., plyometric exercise-based) on total body aBMD and BMC outcomes. In young pediatric cancer survivors, Mogil et al. [22] observed significant effects (P = .05) of a low-magnitude, high-frequency mechanical stimulation during one year, seven days/week and two sessions per day lasting 10 minutes each on total body aBMD Z-scores. The timing of the frequency (twice per day) and adequate intervention duration (one year) could explain these positive findings. This program is not entirely similar to our intervention due to the use of an external active platform and hence, this hampers further comparisons. Similar to our findings, a non-RCT evaluating the effects of a concurrent full-body exercise intervention during six months, three days/week and lasting 55-60 minutes each in survivors did not find significant effects on total body aBMD Z-scores [20]. Although our intervention is specifically designed to improve bone health following the training principles of previous successful interventions in healthy children and adolescents [94,95], it lacks core and upper-body exercises that might have improved muscle strength/mass that could have created the needed stimulus for bone mass to increase, according to the mechanostat theory of Frost [10]. This may also explain why we only found small-sized effects (borderline) on lumbar spine BMC Z-score (per-protocol analysis). In healthy children and adolescents, the mentioned systematic review [9], did show positive effects on lumbar spine aBMD and BMC outcomes. However, in young pediatric cancer survivors, two exercise interventions not primarily focused on improving bone [18] and non-osteogenic [17], in addition to the studies of Mogil et al. [22] and Dubnov-Raz [20], did not observe significant effects on aBMD, volumetric aBMD, age-, sex-, and race-specific aBMD, BMC at lumbar spine. Altogether, our RCT suggests that bone adaptations are site-specific since the observed effects are mainly found at the hip region, which was our main target. Nevertheless, future studies are needed to confirm whether resistance exercise interventions of high impact loading, including supervised full-body exercise sessions, can improve bone health at femoral neck aBMD Z-score and other key regions so that they can be

incorporated into surveillance guidelines and provide a foundation for individualized exercise-oncology plans development, specifically adapted to the needs of the pediatric cancer survivors.

Limitations

The interpretation of the present International Doctoral Thesis should be made in conjunction with some knowledgeable limitations. In **Chapter 4**, the main limitation of the systematic review and meta-analysis was the low number of previously published studies and well-designed RCTs aiming at investigating bone changes in children and adolescents diagnosed with cancer and thus, these findings should be viewed with caution. In **Chapters 5-9**, the cross-sectional designs limited the ability to establish causal relationships. Moreover, yet analyses were controlled for relevant cofounders, it could not be certain that other unmeasured variables could have not influenced these observations. Additionally, given that bone depth is not factored into DXA results, reliance on aBMD systematically could underestimate bone density in shorter individuals. Finally, included survivors were those who elected to enroll in an exercise intervention to improve aBMD. Therefore, they may not be representative of all young pediatric cancer survivors, making the interpretations of our cross-sectional studies potentially vulnerable to selection bias. Finally, in **Chapter 10**, although the adherence with the intervention was monitored using a diary that was monthly reviewed, the exercise sessions were not supervised throughout the intervention. Nevertheless, parents provided the necessary support when needed and research staff kept frequent contact via WhatsApp groups. In fact, we observed higher positive effects when meeting the minimum of the recommended exercise sessions (per-protocol analysis) suggesting that those who reported more sessions performed obtained the greatest benefits. COVID-19 restrictions did not enable this RCT to be conducted under usual settings potentially affecting intensity required and motivation. Moreover, pediatric cancer is a rare disease and hence, recruiting participants is challenging. Future studies, if possible, may test the benefits of a similar resistance exercise intervention in survivors with low aBMD. Additionally, even though we used a parallel-group RCT (1:1) design, we could not control for potential confounding by differences in other factors that considerably influence bone growth such as genetics. We could not determine whether bone health improvements at the hip region are sustained over time following the cessation of our intervention.

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CONCLUSIONS

Chapter 12. Conclusions of the International Doctoral Thesis

Conclusions

This International Doctoral Thesis provides seven specific conclusions that add new insights into the role of the exercise for bone health improvement in young pediatric cancer survivors.

- Specific conclusion I (**Chapter 4**): Our systematic review and meta-analysis indicate that previous exercise interventions were inappropriate and therefore, ineffective to illustrate any beneficial effect on bone of children and adolescents with cancer during and after oncological treatment.
- Specific conclusion II (**Chapter 5**): Region-specific lean mass is consistently the most important positive determinant of all bone parameters. Years from PHV and time from treatment completion are also found to be important positive determinants for the aBMD and HSA parameters. RCTs focusing on bone outcomes of young pediatric cancer survivors should focus on improving region-specific lean mass due to the site-specific adaptations of the skeleton to external loading.
- Specific conclusion III (**Chapter 6**): TV watching time is negatively associated with most bone parameters in peri/post-pubertal survivors, but this association is dependent on lean mass. Noteworthy, survivors watching TV more than one hour per day and with high lean mass present higher bone parameters Z-score than those with low lean mass. These findings underline the need of improving musculoskeletal development while reducing TV watching time after pediatric cancer.
- Specific conclusion IV (**Chapter 7**): The predicted associations of MVPA with higher aBMD are significant at most sites in pre-pubertal young pediatric cancer survivors. In peri/post-pubertal survivors with low MVPA levels, LPA is significantly associated with higher aBMD at all sites. Moreover, replacing MVPA or LPA with SB is significantly associated with lower aBMD at most sites in pre-pubertal and peri/post-pubertal survivors, respectively. These findings suggest that every move counts and underline the benefits of increasing MVPA or LPA to maximize bone regeneration following pediatric cancer treatment completion.
- Specific conclusion V (**Chapter 8**): In a sample of young pediatric cancer survivors who electively enrolled on an intervention study to improve bone health, we identify both upper- and lower-body muscle strength deficits and associations of such deficits with lower aBMD. Further research in cohort studies is needed to validate these

findings so they can be incorporated into surveillance guidelines and provide a foundation for individualized exercise-oncology plans development, specifically adapted to the needs of the patients.

- Specific conclusion VI (**Chapter 9**): Sarcopenia is prevalent in young pediatric cancer survivors and associated with higher risk of low aBMD Z-score. These results suggest that sarcopenia detection in young cancer survivors at early stages after treatment completion could help survivors to be screened for low aBMD Z-score. Further research is still needed to confirm these findings in larger cohort studies so that they could be included in surveillance guidelines.
- Specific conclusion VII (**Chapter 10**): The findings of this RCT show that a 9-month online resistance exercise intervention of high impact loading does not increase femoral neck aBMD Z-score, yet it induces improvements at the hip region in young pediatric cancer survivors. During a sensitive period of life (i.e., childhood) for bone remodeling, these improvements may contribute to reducing the risk of osteopenia/osteoporosis and fractures at this site later in life.

Conclusiones

Esta Tesis Doctoral Internacional ofrece siete conclusiones específicas que aportan nuevos conocimientos sobre el rol del ejercicio físico para la mejora de la salud ósea en jóvenes supervivientes de cáncer.

- Conclusión específica I (**Capítulo 4**): Nuestra revisión sistemática y metaanálisis indica que las intervenciones de ejercicio física previas fueron inapropiadas y, por lo tanto, ineficaces para mostrar algún efecto beneficioso sobre la salud ósea de niños y adolescentes con cáncer durante y después de los tratamientos oncológicos.
- Conclusión específica II (**Capítulo 5**): La masa magra específica a cada región es consistentemente el determinante positivo más importante de todos los parámetros óseos. También encontramos que los años desde el pico de velocidad de crecimiento y el tiempo desde la finalización del tratamiento son determinantes positivos importantes para los parámetros de densidad mineral ósea y geometría de la cadera. Los ensayos controlados y aleatorizados centrados en mejorar los parámetros óseos de jóvenes supervivientes de cáncer deberían centrarse en mejorar la masa magra específica a cada región debido a las adaptaciones específicas del esqueleto a las cargas externas.
- Conclusión específica III (**Capítulo 6**): El tiempo frente a la televisión se asocia negativamente con la mayoría de los parámetros óseos en los supervivientes peri/postpuberales, pero esta asociación es dependiente de la masa magra. Cabe destacar que los supervivientes que ven la televisión más de una hora al día y con una masa magra alta presentan parámetros óseos Z-score más altos que aquellos con masa magra baja. Estos hallazgos identifican la necesidad de mejorar el desarrollo musculoesquelético y al mismo tiempo reducir el tiempo frente a la televisión después del cáncer pediátrico.
- Conclusión específica IV (**Capítulo 7**): Las asociaciones de la actividad física moderada-vigorosa con una mayor densidad mineral ósea son significativas en la mayoría de las regiones en jóvenes supervivientes prepuberales de cáncer. En aquellos peri/postpuberales con niveles bajos de actividad física moderada-vigorosa, la actividad física ligera se asocia significativamente con una mayor densidad mineral ósea en todas las regiones. Además, reemplazar la actividad física moderada-vigorosa o ligera por comportamientos sedentarios se asocia significativamente con una menor densidad mineral ósea en la mayoría de las regiones en los supervivientes prepuberales y

peri/pospuberales, respectivamente. Estos hallazgos sugieren que cada movimiento cuenta y señalan los beneficios de aumentar actividad física moderada-vigorosa o ligera para maximizar la regeneración ósea después de completar el tratamiento del cáncer pediátrico.

- Conclusión específica V (**Capítulo 8**): En nuestra muestra de jóvenes supervivientes de cáncer que se inscribieron de manera electiva a un estudio de intervención para mejorar la salud ósea, identificamos déficits de fuerza muscular en la parte superior e inferior del cuerpo y asociaciones de dichos déficits con una densidad mineral ósea más baja. Se necesitan más estudios de grandes cohortes para validar estos hallazgos de modo que puedan incorporarse a las pautas de vigilancia y proporcionar una base para el desarrollo de planes de ejercicio físico individualizados, adaptados específicamente a las necesidades de los pacientes oncológicos.
- Conclusión específica VI (**Capítulo 9**): La sarcopenia es prevalente en jóvenes supervivientes de cáncer y se asocia con un mayor riesgo de tener una peor salud ósea. Estos resultados sugieren que la detección de sarcopenia en jóvenes supervivientes de cáncer en etapas tempranas después de completar el tratamiento podría ayudar a los supervivientes a ser evaluados para detectar antes una peor salud ósea. Aún se necesitan más investigaciones para confirmar estos hallazgos en estudios con cohortes más grandes para que puedan incluirse en las pautas de vigilancia.
- Conclusión específica VII (**Capítulo 10**): Una intervención de ejercicio físico de fuerza y alto impacto en línea durante nueve meses de duración no es efectiva para aumentar la densidad mineral ósea del cuello del fémur, aunque se observan mejoras en la salud ósea de la región de la cadera en jóvenes supervivientes de cáncer. Durante un período sensible para el desarrollo óseo como el crecimiento, estas mejoras pueden contribuir a reducir el riesgo de osteopenia/osteoporosis y fracturas en esta región en la etapa adulta. Estudios futuros son necesarios para confirmar si una intervención supervisada de ejercicio físico de fuerza del cuerpo completo y alto impacto puede aumentar la densidad mineral ósea del cuello del fémur y otras regiones clave en esta población.

FUTURE PERSPECTIVES

Chapter 13. Future perspectives

Future perspectives

Despite the meaningful advancements in exercise pediatric oncology and bone health, there are still many unanswered questions that warrant further investigation to gain a deeper understanding of the effects of exercise on bone health, laying the foundations for individualized strategies and guidelines, specifically adapted to the needs of the patients. Future research should focus on the following areas:

- Potential synergistic benefits: There is a need to determine whether combining similar exercise programs and pharmacologic interventions are more effective at preventing bone loss among children and adolescents during cancer treatment and/or improving bone health after cancer treatment completion as well as in those adolescents and young adults who have achieved skeletal maturity.
- Residual effect: To determine whether bone health improvements are sustained over time following the cessation of a resistance exercise intervention of high impact loading.
- Barriers to adherence: Elucidating which demographics, treatment exposure, lifestyle factors and health-related conditions might improve the adherence to long-lasting exercise programs to improve bone health.
- Sex-specific differences: To gain a deeper understanding of potential sex-specific differences on the effects of a resistance exercise intervention of high impact loading on bone health.
- Clinical meaningfulness of new technological advances: The creation of age- and sex-specific pediatric reference values of data from peripheral quantitative computed tomography, DXA-derived hip structural analyses and trabecular bone score will enable to address their clinical meaningfulness.

ANNEXES

Chapter 14. Manuscripts derived from the present International Doctoral Thesis

Marmol-Perez A, Ubago-Guisado E, Rodriguez-Solana A, Gil-Cosano JJ, Martinez-Vizcaino V, Cavero-Redondo I, Ruiz JR, Gracia-Marco L. Effect of exercise on bone health in children and adolescents with cancer during and after oncological treatment: A systematic review and meta-analysis. *Frontiers in Physiology*, 2023. PMID: 37035662. DOI: 10.3389/fphys.2023.1088740.

Marmol-Perez A, Ubago-Guisado E, Llorente-Cantarero FJ, Vlachopoulos D, Rodriguez-Solana A, Gil-Cosano JJ, Ruiz JR, Gracia-Marco L. Determinants of bone parameters in young paediatric cancer survivors: the iBoneFIT project. Pediatric Research, 2023. PMID: 37202528. DOI: 10.1038/s41390-023-02645-8.

Marmol-Perez A, Ubago-Guisado E, Llorente-Cantarero FJ, Cadenas-Sanchez C, Andrea Rodriguez-Solana, Gil-Cosano JJ, Pascual-Gázquez JF, Ruiz JR, Gracia-Marco L. Lean Mass Attenuates Negative Associations of Watching Television with Bone Parameters in Young Paediatric Cancer Survivors. Revised Version Under Review (Pediatric Research).

Marmol-Perez A, Migueles JH, Ubago-Guisado E, Gil-Cosano JJ, Rodriguez-Solana A, Redondo-Tébar A, Llorente-Cantarero FJ, Labayen I, Ortega FB, Ruiz JR, Gracia-Marco L. Every Move Counts to Improve Bone Health at Clinical Sites in Young Pediatric Cancer Survivors: The iBoneFIT Project. Medicine and Science in Sports and Exercise, 2024. PMID: 38306313. DOI: 10.1249/MSS.0000000000003397.

Marmol-Perez A, Gil-Cosano JJ, Ubago-Guisado E, Llorente-Cantarero FJ, Pascual-Gázquez JF, Ness KK, Martinez-Vizcaino V, Ruiz JR, Gracia-Marco L. Muscle strength deficits are associated with low bone mineral density in young pediatric cancer survivors: The iBoneFIT project. Journal of Sport and Health Science, 2024. PMID: 38219958. DOI: 10.1016/j.jshs.2024.01.003.

Marmol-Perez A, Ubago-Guisado E, Gil-Cosano JJ, Llorente-Cantarero FJ, Pascual-Gázquez JF, Muñoz-Torres M, Martinez-Vizcaino V, Ness KK, Ruiz JR, Gracia-Marco L. Comorbid

Sarcopenia and Low Bone Mineral Density in Young Pediatric Cancer Survivors. Revised Version Under Review (Journal of Cachexia, Sarcopenia and Muscle).

Marmol-Perez A. Effects of an exercise program on bone health in young pediatric cancer survivors: The iBoneFIT Randomized Controlled Trial. In Preparation.

Curriculum Vitae

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EDUCATION

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- **2020-2021:** Expert's degree in Exercise and Oncological Patients, Autonomic Madrid University, Spain.
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PREVIOUS AND CURRENT POSITIONS

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INTERNATIONAL FELLOWSHIPS

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PERSONAL GRANTS

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- **2021:** Predoctoral FPU Research fellow (FPU20/05530). Department of Physical Education and Sports, Faculty of Sport Sciences. University of Granada, Granada, Spain.

- **2021:** Research initiation fellow for official master's students with the Adaptative Physiology Group, Department of Cellular Biology, Physiology and Immunology at the Biology Faculty, Barcelona University, Spain.

RESEARCH EXPERIENCE

- **2024:** Associations of Physical Activity, Cardiorespiratory Fitness and Muscle Strength with Occupational Balance in Adult Cancer Survivors. Programa de Proyectos de Investigación Precompetitivos para Jóvenes Investigadores. (University of Granada). 01/01/2024-31/12/2024. 1.000 €. PI: Andres Marmol-Perez.
- **2021-2024**: REBOTA-Ex trial: Regulating bone metabolism through exercise in paediatric cancer survivors. Ministerio de Ciencia e Innovación (ref. PID2020-117302RA-I00). (Universidad de Granada). 169.400 €. PI: Luis Gracia-Marco.
- **2021-2024**: The iBoneFIT project: the effect of an online exercise programme on bone health in childhood cancer survivors (iBoneFIT): A multi-centre randomized controlled trial. Funded by a fellowship from "la Caixa" Foundation (ID 100010434). The fellowship code is LCF/BQ/PR19/11700007: 297,294 €. Funded by Spanish Ministry of Economy and competitiveness: 100,000€. PI: Luis Gracia-Marco.
- **2021-2023:** The DIVA project: Diurnal variation of the effect of aerobic exercise on glucose metabolism and fat oxidation in humans. Spanish Ministry of Culture and Sport, Consejo Superior de Deportes, Plan de Recuperación, Transformación y Resiliencia, Unión Europea, Nex Generation EU y Ayudas europeas a proyectos de investigación aplicada a la Actividad Física Beneficiosa para la Salud y la Medicina Deportiva (EXP_77437). (Universidad de Granada): 143.264 €. PI: Francisco J. Amaro-Gahete.

RESEARCH PUBLICATIONS

- **Marmol-Perez, Andres**; Corres, Pablo; Fernández-Escabias, Manuel; Carrilho-Candeias, Sofia; R Ruiz, Jonatan; Amaro-Gahete, Francisco J; Carneiro-Barrera, Almudena. Impact of Multidisciplinary Prehabilitation Interventions on Postoperative Hospital Length of Stay and Functional Capacity in Patients Undergoing Resection of Colorectal Cancer: A Systematic Review and Meta-analysis. Dis Colon Rectum. 10.1097/DCR.0000000000003268. (3.2 IF; Surgery; Q1, 49/290).

- **Marmol-Perez, Andres**; Migueles, Jairo H; Ubago-Guisado, Esther; et al; Gracia-Marco, Luis. 2024. Every Move Counts to Improve Bone Health at Clinical Sites in Young Pediatric Cancer Survivors: The iBoneFIT Project. Med Sci Sports Exerc. https://doi.org/10.1249/MSS.0000000000003397. (4.1 IF; Sport Sciences; Q1, 11/127).
- **Marmol-Perez, Andres**; Gil-Cosano, Jose J; Ubago-Guisado, Esther; et al; Gracia-Marco, Luis. 2024. Muscle strength deficits are associated with low bone mineral density in young pediatric cancer survivors: The iBoneFIT project. J Sport Health Sci. 13(3):419-427. https://doi.org/10.1016/j.jshs.2024.01.003. (9.7 IF; Sport Sciences; D1, 2/127).
- **Marmol-Perez, Andres**; Ubago-Guisado, Esther; Llorente-Cantarero, Francisco J; Vlachopoulos, Dimitris; Rodriguez-Solana, Andrea; Gil-Cosano, Jose J; Ruiz, Jonatan R; Gracia-Marco, Luis. 2023. Determinants of bone parameters in young paediatric cancer survivors: the iBoneFIT project. Pediatr Res. 94-4. https://doi.org/10.1038/s41390-023-02645-8. (3.1 IF; Pediatrics; Q1, 25/186).
- **Marmol-Perez, Andres**; Ubago-Guisado, Esther; Rodriguez-Solana, Andrea; Gil-Cosano, Jose J; Martinez-Vizcaino, Vicente; Cavero-Redondo, Ivan; Ruiz, Jonatan R; Gracia-Marco, Luis. 2023. Effect of exercise on bone health in children and adolescents with cancer during and after oncological treatment: A systematic review and meta-analysis. Front Physiol. 14, pp.1088740. https://doi.org/10.3389/fphys.2023.1088740. (3.2 IF; Physiology; Q2, 24/85).
- Rodriguez-Solana, Andrea; Gracia-Marco, Luis; Llorente-Cantarero, Francisco J; Cadenas-Sanchez, Cristina; **Marmol-Perez, Andres**; Gil-Cosano, Jose J; Moliner-Urdiales, Diego; Ubago-Guisado, Esther. 2023. Is higher physical fitness associated with better psychological health in young pediatric cancer survivors? A cross-sectional study from the iBoneFIT project. Scand J Med Sci Sports. 33-7, pp.1157-1167. https://doi.org/10.1111/sms.14345. (3.5 IF; Sport Sciences; Q1, 15/127).
- Amaro-Gahete, Francisco J; Jurado, Javier; Cisneros, Andrea; et al; Carneiro-Barrera, Almudena; **Marmol-Perez, Andre**; Osuna-Prieto. Francisco J; Fernández-Escabias, Manuel; Salcedo, Estela; Hermán-Sánchez, Natalia; Gahete, Manuel D; Aparicio, Virginia A, González-Callejas, Cristina; Mirón Pozo, Benito; Ruiz, Jonatan R; Nestares, Teresa; Carneiro-Barrera, Almudena. 2022. Multidisciplinary Prehabilitation and Postoperative Rehabilitation for Avoiding Complications in Patients Undergoing Resection of Colon Cancer: Rationale, Design, and Methodology of the ONCOFIT

Study. Nutrients. 14-21, pp.4647. https://doi.org/10.3390/nu14214647. (5.9 IF; Nutrition & Dietetics; Q1, 17/88).

CONFERENCE ABSTRACTS

Only the conference abstracts as first author from the last two years are included:

- **Marmol-Perez, Andres**; Ubago-Guisado, Esther; Gil-Cosano, Jose J; Rodriguez-Solana, Andrea; Pascual-Gázquez, Juan Francisco; Llorente-Cantarero, Francisco J; Martinez-Vizcaino, Vicente; Muñoz-Torres, Manuel; Ruiz, Jonatan R; Gracia-Marco, Luis. Comorbid sarcopenia status and bone mineral density in young survivors of cancer. The iBoneFIT Project. International Conference on Children's Bone Health. 2024. Poster.
- **Marmol-Perez, Andres**; Ubago-Guisado, Esther; Gil-Cosano, Jose J; Pascual-Gázquez, Juan Francisco; Llorente-Cantarero, Francisco J; Armstrong, Gregory T; Muñoz-Torres, Manuel; Martinez-Vizcaino, Ness, Kirsten K; Ruiz, Jonatan R; Gracia-Marco, Luis. Risk of low bone mineral density in young pediatric cancer survivors with sarcopenia. American College of Clinical Oncology Annual Meeting. 2024. Poster.
- **Marmol-Perez, Andres**; Ubago-Guisado, Esther; Gil-Cosano, Jose J; Pascual-Gázquez, Juan Francisco; Llorente-Cantarero, Francisco J; Armstrong, Gregory T; Muñoz-Torres, Manuel; Martinez-Vizcaino, Vicente; Ness, Kirsten K; Ruiz, Jonatan R; Gracia-Marco, Luis. Risk of low bone mineral density in young pediatric cancer survivors with sarcopenia. American College of Clinical Oncology Annual Meeting. 2024. Poster.
- **Marmol-Perez, Andres**; Ubago-Guisado, Esther; Gil-Cosano, Jose J; Rodriguez-Solana, Andrea; Llorente-Cantarero, Francisco J; Pascual-Gázquez, Juan Francisco; Cadenas-Sanchez, Cristina; Ness, Kirsten K; Labayen, Idoia; Martinez-Vizcaino, Vicente; Ortega, Francisco B. Ortega, Ruiz, Jonatan R; Gracia-Marco, Luis. Effects Of An Exercise Program On Bone Health In Pediatric Cancer Survivors: Randomized Controlled Trial. 2024 American College of Sports Medicine Annual Meeting. 2024. Poster.
- **Marmol-Perez, Andres**; Ubago-Guisado, Esther; Gil-Cosano, Jose J; Rodriguez-Solana, Andrea; Redondo-Tébar, Andrés; Llorente-Cantarero, Francisco J; Pascual-Gázquez, Juan Francisco; Martinez-Vizcaino, Vicente; Ortega Costa, María José; Muñoz-Torres, Manuel; Ruiz, Jonatan R; Gracia-Marco, Luis. Sarcopenia y baja

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- **Marmol-Perez, Andres**; Ubago-Guisado, Esther; Llorente-Cantarero, Francisco J; Vlachopoulos, Dimitris; Rodriguez-Solana, Andrea; Gil-Cosano, Jose J; Ruiz, Jonatan R; Gracia-Marco, Luis. Determinantes de la Salud Ósea en Supervivientes de Cáncer Infantil: El Proyecto iBoneFIT. Annual international congress of PhD students. Universidad Miguel Hernández de Elche. 2023. Oral communication.
- **Marmol-Perez, Andres**; Clavero-Jimeno, Antonio; Ruiz, Jonatan R; Alcantara, Juan MA. Estimation of Oxygen Consumption through the Predictive Equations of walking compared to Indirect Calorimetry at different intensities. Annual international congress of PhD students. Universidad Miguel Hernández de Elche. 2023. Oral communication.
- **Marmol-Perez, Andres**; Rodriguez-Solana, Andrea; Ubago-Guisado, Esther; Gracia-Marco, Luis. Ejercicio físico y salud ósea tras cáncer infantil en la Noche Europea de los Investigadores. Noche Europea de los Investigadores. Universidad de Granada. 2022. España. Oral communication.
- **Marmol-Perez, Andres**; Rodriguez-Solana, Andea; Gil-Cosano, Jose J; Ubago-Guisado, Esther; Pascual-Gázquez, Juan Francisco; Ruiz, Jonatan R; Gracia-Marco, Luis. Association of television viewing time with bone health in children and

adolescents cancer survivors: the iBoneFIT study. III International CERFA Cancer Symposium: Connecting Spanish Researchers around the world. CERFA. 2022. Poster.

- **Marmol-Perez, Andres**; Gil-Cosano, Jose J; Ubago-Guisado, Esther; Rodriguez-Solana, Andrea; Llorente-Cantarero, Francisco J; Pascual-Gázquez, Juan Francisco; Ortega-Acosta, Maria Jose; Gracia-Marco, Luis. Asociación entre la maduración somática y la salud ósea en niños y adolescentes supervivientes de cáncer infantil: El rol de la masa magra. Resultados preliminares del estudio iBoneFIT. Symposium EXERNET Red Española de Investigación en Ejercicio físico y Salud. Universidad de Castilla-La Mancha. 2021. España. Oral communication.

BOOK CHAPTER

- **2022.** Exercise and childhood cancer. What does science say? Dykinson, Madrid, Spain.

REVIEWER ACTIVITY

- Reviewer of the JCR-indexed Medicine & Science in Sports & Exercise.

UNIVERSITY TEACHING

- **2021-2024.** Functional Anatomy of the Locomotor System (120 hours of teaching, 12 ECTS [European Credit Transfer and Accumulation System] credit). Degree/Bachelor: Sport and Exercise Sciences, University of Granada (Spain).

SUPERVISION

- **2022-2023:** Supervisor for 3 Master's Thesis (Master's degree in in Researching in Physical Activity and Sports), University of Granada, Spain.

PRIZES AND AWARDS

- **2023:** Fulbright Scholarship for a nine-month predoctoral stay at St. Jude Children's Research Hospital (Memphis, US).
- **2021:** Extraordinary Prize of the Master's degree in Integrative Physiology, Barcelona University, Spain.
- **2020:** Award for Excellence in Academic Performance of Undergraduate Students of the Huelva University 2018/19 academic year. Funded by the Santander Bank.

- **2017:** Research initiation fellow for undergraduate students with the Integrated Didactics. Department of Education Faculty, Huelva University, Spain.

LANGUAGES

- Certificate in Advanced English (CAE) by Cambridge. Council of Europe level C1.

LAST PAGE