European Society for Paediatric Research
Society for Pediatric Research
www.nature.com/pr

CLINICAL RESEARCH ARTICLE

Check for updates

Determinants of bone parameters in young paediatric cancer survivors: the iBoneFIT project

Andres Marmol-Perez[1], Esther Ubago-Guisado[1,2]✉, Francisco J. Llorente-Cantarero[3,4,5], Dimitris Vlachopoulos[6], Andrea Rodriguez-Solana[1], Jose J. Gil-Cosano[1,7], Jonatan R. Ruiz[1,2,4] and Luis Gracia-Marco[1,2,4]

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 multicentre 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 peak height velocity (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 areal bone mineral density (aBMD), all hip geometry parameters and Trabecular Bone Score ($\beta = 0.400$–0.775, $p \le 0.05$). 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 ($\beta = 0.327$–0.398, $p \le 0.05$; $\beta = 0.135$–0.221, $p \le 0.05$), respectively.

CONCLUSION: Region-specific lean mass was consistently the most important positive determinant of all bone parameters, except for total hip aBMD, all Hip Structural Analysis parameters and Trabecular Bone Score.

Pediatric Research; https://doi.org/10.1038/s41390-023-02645-8

IMPACT:

- The findings of this study indicate that region-specific lean mass is consistently the most important positive determinant of bone health in young paediatric cancer survivors.
- Randomised clinical trials focused on improving bone parameters of this population should target at region-specific lean mass due to the site-specific adaptations of the skeleton to external loading following paediatric cancer treatment.
- After paediatric cancer diagnosis, years from peak height velocity (somatic maturity) is critical for bone development.

INTRODUCTION

Paediatric cancer survival has experienced an unparalleled increase during the last few years.[1] The 5-year survivorship rate for all paediatric cancers has approached 85%.[2] However, a low areal bone mineral density (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 a 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

[1]Department of Physical Education and Sports, Faculty of Sports Science, Sport and Health University Research Institute (iMUDS), University of Granada, Granada, Spain. [2]Instituto de Investigación Biosanitaria, ibs.Granada, Granada, Spain. [3]Instituto de Investigación Biomédica Maimonides (IMIBIC), Córdoba, España. [4]CIBER de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain. [5]Departamento de Didácticas Específicas, Facultad de Educación, Universidad de Córdoba, Córdoba, España. [6]Centro de Investigación sobre Ejercicio y Salud Infantil, Universidad de Exeter, Exeter, UK. [7]Department of Communication and Education, Universidad Loyola Andalucía, Dos Hermanas, Sevilla, Spain. ✉email: estherug@ugr.es

Received: 19 December 2022 Revised: 18 April 2023 Accepted: 20 April 2023
Published online: 18 May 2023

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 Dual-energy X-ray Absorptiometry (DXA) but also other DXA-derived parameters obtained from the Hip Structural Analysis and the textural analysis of the lumbar spine. We hypothesised that region-specific lean mass and years from peak height velocity (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 6–18 years old; (ii) not currently receiving treatment for cancer; (iii) diagnosed 1 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] (Supplementary Table 1, see the section on Supplementary materials given at the end of this article). 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 (Supplementary Table 2), 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 on their non-dominant wrist for at least 7 consecutive days (24 h 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). Moderate-to-vigorous physical activity (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 h and the participants wore it for at least 16 h. In addition, 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: $R \times y \times a$, 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 by using the handgrip test (performed twice by each hand and the best scores were averaged) and lower-body power by 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: 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: Hip geometry parameters at the narrowest point of the femoral neck were determined using Hip Structural Analysis 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), which 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: The iNsight Software (Medimaps, research version 3.0, Pessac, France) 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] Trabecular Bone Score 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 Trabecular Bone Score has been reported to be between 1.7 and 2.1% for lumbar spine aBMD.[35] Although Trabecular Bone Score has been mostly used in the adult population,[36] its use has been extended into paediatric population in the last few years.[37–39]

Statistical analysis

The normal distribution of the raw variables was checked and verified using a visual check of histograms, skewness and kurtosis values, Shapiro–Wilk test, Q–Q and box plots. Descriptive data were illustrated as mean and standard deviation. Collinearity was checked for the variables using the variance inflation factor 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, Hip Structural Analysis parameters and Trabecular Bone Score. 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 (Supplementary Table 3), 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 were presented, R^2 was calculated by 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 the 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%) (Supplementary Table 2).

Determinants of areal bone mineral density

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 ($\beta = 0.400–0.517$, $sr^2 = 0.017–0.023$, $p \le 0.05$), except for total hip ($p > 0.05$). Years from PHV were positively associated with aBMD at total body less head, legs and arms ($\beta = 0.327–0.398$, $sr^2 = 0.016–0.027$, $p \le 0.05$). Past bone-specific physical activity was positively associated with aBMD at total hip and arms ($\beta = 0.097–0.162$, $sr^2 = 0.006–0.018$, $p \le 0.05$). Being female was positively associated with aBMD at lumbar spine ($\beta = 0.182$, $sr^2 = 0.017$, $p \le 0.05$). Time from treatment completion was positively associated with aBMD at total hip ($\beta = 0.221$, $sr^2 = 0.037$, $p \le 0.05$). Fat mass was positively associated with aBMD at arms ($\beta = 0.232$, $sr^2 = 0.028$, $p \le 0.05$). 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 Supplementary Fig. 1.

Determinants of Hip Structural Analysis parameters and Trabecular Bone Score

In the multivariate regression analysis of the Hip Structural Analysis (Table 3), the predictors explained 43.9–64.6% (on average, 54.25%) of the variance in the Hip Structural Analysis and Trabecular Bone Score. Region-specific lean mass was the strongest significant predictor and was positively associated with all Hip Structural Analysis parameters ($\beta = 0.628–0.775$, $sr^2 = 0.049–0.071$, $p \le 0.05$). Being female (positively) and upper-body strength (negatively) were associated with Trabecular Bone Score ($\beta = 0.245$ and -0.443, $sr^2 = 0.031$ and 0.023, $p \le 0.05$, respectively). Time from treatment completion was positively associated with narrow neck cross-sectional area ($\beta = 0.135$, $sr^2 = 0.014$, $p \le 0.05$). 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 Hip Structural Analysis parameters nor spine Trabecular Bone Score (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 Supplementary Fig. 2.

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 the 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, Hip Structural Analysis parameters and Trabecular Bone Score.

Determinants of areal bone mineral density

Previous findings in healthy population with similar models of determinants explained 40–83% 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 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 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

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	25,713.2 (10,381.1)	116	23,937.8 (8962.5)	50	27,058.1 (11,218.3)	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	14,296.0 (5561.0)	116	13,611.4 (5129.4)	50	14,814.7 (5852.0)	66
Fat mass (g)						
Total body less head	14,899.1 (8336.3)	116	16,161.2 (9695.7)	50	13,942.9 (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 regression 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

Standardised β coefficient, R^2 (Stein's equation), squared semi-partial correlation and p value are provided (boldface indicates $p < 0.050$).
sr^2 squared semi-partial correlation, *aBMD* areal bone mineral density, *TBLH* total body less head, *FN* femoral neck, *LS* lumbar spine, *PA* physical activity.

Table 3. Multiple regression 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

Standardised β coefficient, R^2 (Stein's equation), squared semi-partial correlation and *p* value are provided (boldface indicates $p < 0.050$).
sr^2 squared semi-partial 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.

does not seem noticeable, perhaps because of the strong relationship of region-specific lean mass. In addition, 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 of 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, Hip Structural Analysis parameters and Trabecular Bone Score 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 Hip Structural Analysis can provide a 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 Hip Structural Analysis 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 Hip Structural Analysis parameters. However, the differences in the population characteristics, evaluation techniques and 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 the findings of a previous review which identified that following the 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 Hip Structural Analysis parameters, the strongest determinant for the Trabecular Bone Score 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 Trabecular Bone Score at baseline was significantly higher in females than males (Trabecular Bone Score in males: 1.345 ± 0.095; and females: 1.370 ± 0.099).[60] This shows the beneficial effects of time-off therapy on bone impairments caused by oncological treatment. However, the limited number of studies using Trabecular Bone Score 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 Trabecular Bone Score, 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 on young paediatric cancer survivors examining the determinants of aBMD, Hip Structural Analysis parameters and Trabecular Bone Score. Many predictors have been taken into account, adjusting their effects on each other. In addition, this study specifically uses region-specific lean mass as a predictor because of the site-specific adaptations of the skeleton during growth.[62]

In 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 Hip Structural Analysis 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.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are not publicly available due to the fact that the iBoneFIT project has not finished yet but are available from the corresponding author on reasonable request.

REFERENCES

1. Miller, K. D. et al. Cancer statistics for adolescents and young adults, 2020. *CA Cancer J. Clin.* **70**, 443–459 (2020).
2. Siegel, R. L. et al. Cancer statistics, 2023. *CA Cancer J. Clin.* **73**, 17–48 (2023).
3. Wilson, C. L. & Ness, K. K. Bone mineral density deficits and fractures in survivors of childhood cancer. *Curr. Osteoporos. Rep.* **11**, 329–337 (2013).
4. Marcucci, G. et al. Bone health in childhood cancer: review of the literature and recommendations for the management of bone health in childhood cancer survivors. *Ann. Oncol.* **30**, 908–920 (2019).
5. Kelly, P.M. & Pottenger, E. Bone health issues in the pediatric oncology patient. *Semin. Oncol. Nurs.* **38**, 151275. https://doi.org/10.1016/J.SONCN.2022.151275 (2022).
6. Weaver, C. M. et al. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. *Osteoporos. Int.* **27**, 1281–1386 (2016).
7. Gómez-Bruton, A., Matute-Llorente, Á., González-Agüero, A., Casajús, J. A. & Vicente-Rodríguez, G. Plyometric exercise and bone health in children and adolescents: a systematic review. *World J. Pediatr.* **13**, 112–121 (2017).
8. Othman, F., Guo, C. Y., Webber, C., Atkinson, S. A. & Barr, R. D. Osteopenia in survivors of Wilms tumor. *Int J. Oncol.* **20**, 827–833 (2002).
9. Chen, J. H., Liu, C., You, L. & Simmons, C. A. Boning up on Wolff's Law: mechanical regulation of the cells that make and maintain bone. *J. Biomech.* **43**, 108–118 (2010).
10. Jarfelt, M., Fors, H., Lannering, B. & Bjarnason, R. Bone mineral density and bone turnover in young adult survivors of childhood acute lymphoblastic leukaemia. *Eur. J. Endocrinol.* **154**, 303–309 (2006).
11. Zymbal, V., Baptista, F., Letuchy, E. M., Janz, K. F. & Levy, S. M. Mediating effect of muscle on the relationship of physical activity and bone. *Med. Sci. Sports Exerc.* **51**, 202–210 (2019).
12. Mostoufi-Moab, S. & Ward, L. M. Skeletal morbidity in children and adolescents during and following cancer therapy. *Horm. Res. Paediatr.* **91**, 137–151 (2019).
13. Huncharek, M., Muscat, J. & Kupelnick, B. Impact of dairy products and dietary calcium on bone-mineral content in children: results of a meta-analysis. *Bone* **43**, 312–321 (2008).
14. Rønne, M. S. et al. Bone mass development in childhood and its association with physical activity and vitamin D levels. The CHAMPS-Study DK. *Calcif. Tissue Int.* **104**, 1–13 (2019).
15. Choudhary, A., Chou, J., Heller, G. & Sklar, C. Prevalence of vitamin D insufficiency in survivors of childhood cancer. *Pediatr. Blood Cancer* **60**, 1237–1239 (2013).
16. Zhang, F. F., Saltzman, E., Must, A. & Parsons, S. K. Do childhood cancer survivors meet the diet and physical activity guidelines? A review of guidelines and literature. *Int. J. Child Health Nutr.* **1**, 44–58. https://doi.org/10.6000/1929-4247.2012.01.01.06 (2012).
17. Vlachopoulos, D. et al. Determinants of bone outcomes in adolescent athletes at baseline: The PRO-BONE Study. *Med. Sci. Sports Exerc.* **49**, 1389–1396 (2017).

18. Gil-Cosano, J. J. et al. The effect of an online exercise programme on bone health in paediatric cancer survivors (iBoneFIT): study protocol of a multi-centre randomized controlled trial. *BMC Public Health* **20**, 1520 (2020).
19. Vandenbroucke, J. P. et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med.* **4**, 1628–1654 (2007).
20. Moore, S. A. et al. Enhancing a somatic maturity prediction model. *Med. Sci. Sports Exerc.* **47**, 1755–1764 (2015).
21. Gurney, J. G. et al. Bone mineral density among long-term survivors of childhood acute lymphoblastic leukemia: results from the St. Jude Lifetime Cohort Study. *Pediatr. Blood Cancer* **61**, 1270–1276 (2014).
22. Migueles, J. H. et al. Comparability of published cut-points for the assessment of physical activity: Implications for data harmonization. *Scand. J. Med. Sci. Sports* **29**, 566–574 (2019).
23. Evenson, K. R., Catellier, D. J., Gill, K., Ondrak, K. S. & McMurray, R. G. Calibration of two objective measures of physical activity for children. *J. Sports Sci.* **26**, 1557–1565 (2008).
24. Weeks, B. K. & Beck, B. R. The BPAQ: a bone-specific physical activity assessment instrument. *Osteoporos. Int* **19**, 1567–1577 (2008).
25. Ruiz, J. R. et al. Field-based fitness assessment in young people: the ALPHA health-related fitness test battery for children and adolescents. *Br. J. Sports Med.* **45**, 518–524 (2011).
26. Ruiz, J. R. et al. Predictive validity of health-related fitness in youth: a systematic review. *Br. J. Sports Med.* **43**, 909–923 (2009).
27. Julián Almárcegui, C. et al. Validity of a food-frequency questionnaire for estimating calcium intake in adolescent swimmers. *Nutr. Hosp.* **32**, 1773–1779 (2015).
28. Bolek-Berquist, J. et al. Use of a questionnaire to assess vitamin D status in young adults. *Public Health Nutr.* **12**, 236–243 (2009).
29. Shuhart, C. R. et al. Executive Summary of the 2019 ISCD Position Development Conference on Monitoring Treatment, DXA Cross-calibration and Least Significant Change, Spinal Cord Injury, Peri-prosthetic and Orthopedic Bone Health, Transgender Medicine, and Pediatrics. *J. Clin. Densitom.* **22**, 453–471 (2019).
30. Johnson, J. & Dawson-Hughes, B. Precision and stability of dual-energy X-ray absorptiometry measurements. *Calcif. Tissue Int.* **49**, 174–178 (1991).
31. Beck, T. J., Ruff, C. B., Warden, K. E., Scott, W. W. & Rao, G. U. Predicting femoral neck strength from bone mineral data. A structural approach. *Invest. Radiol.* **25**, 6–18 (1990).
32. Khoo, B. C. C. et al. In vivo short-term precision of hip structure analysis variables in comparison with bone mineral density using paired dual-energy X-ray absorptiometry scans from multi-center clinical trials. *Bone* **37**, 112–121 (2005).
33. Hans, D., Goertzen, A. L., Krieg, M. A. & Leslie, W. D. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. *J. Bone Min. Res.* **26**, 2762–2769 (2011).
34. Pothuaud, L. et al. Evaluation of the potential use of trabecular bone score to complement bone mineral density in the diagnosis of osteoporosis: a preliminary spine BMD-matched, case-control study. *J. Clin. Densitom.* **12**, 170–176 (2009).
35. Silva, B. C. et al. Trabecular bone score: a noninvasive analytical method based upon the DXA image. *J. Bone Min. Res.* **29**, 518–530 (2014).
36. Shawwa, K. et al. Predictors of trabecular bone score in school children. *Osteoporos. Int.* **27**, 703–710 (2016).
37. Del Rio, L., Di Gregorio, S. & Winzenrieth, R. WCO-IOF-ESCEO Seville 2014. *Osteoporos. Int.* **25**(Suppl 2), 73–445 (2014).
38. Winzenrieth, R., Cormier, C., DiGregorio, S. & Del Rio, L. Influence of age and gender on spine bone density and TBS microarchitectural texture parameters in infants. *Bone Abstracts* **2**, LB1. https://doi.org/10.1530/BONEABS.2.LB1 (2013).
39. Guagnelli, M. A. et al. Bone age as a correction factor for the analysis of trabecular bone score (TBS) in children. *Arch. Osteoporos.* **14**, 26. https://doi.org/10.1007/S11657-019-0573-6 (2019).
40. Macdonald, H., Kontulainen, S., Petit, M., Janssen, P. & McKay, H. Bone strength and its determinants in pre- and early pubertal boys and girls. *Bone* **39**, 598–608 (2006).
41. Davies, J. H., Evans, B. A. J. & Gregory, J. W. Bone mass acquisition in healthy children. *Arch. Dis. Child* **90**, 373–378 (2005).
42. Agostinete, R. R. et al. The mediating role of lean soft tissue in the relationship between somatic maturation and bone density in adolescent practitioners and non-practitioners of sports. *Int. J. Environ. Res. Public Health* **18**, 3008 (2021).
43. Stevens, J. P. *Applied Multivariate Statistics for the Social Sciences* (Lawrence Erlbaum, Mahwah, NJ, 2002).
44. Daly, R. M., Stenevi-Lundgren, S., Linden, C. & Karlsson, M. K. Muscle determinants of bone mass, geometry and strength in prepubertal girls. *Med. Sci. Sports Exerc.* **40**, 1135–1141 (2008).
45. Högler, W. et al. Incidence of skeletal complications during treatment of childhood acute lymphoblastic leukemia: comparison of fracture risk with the General Practice Research Database. *Pediatr. Blood Cancer* **48**, 21–27 (2007).
46. Lim, J. S. et al. Young age at diagnosis, male sex, and decreased lean mass are risk factors of osteoporosis in long-term survivors of osteosarcoma. *J. Pediatr. Hematol. Oncol.* **35**, 54–60 (2013).
47. Muszynska-Roslan, K., Konstantynowicz, J., Krawczuk-Rybak, M. & Protas, P. Body composition and bone mass in survivors of childhood cancer. *Pediatr. Blood Cancer* **48**, 200–204 (2007).
48. Muszynska-Roslan, K. et al. Bone mineral density in pediatric survivors of Hodgkin and non-Hodgkin lymphomas. *Adv. Med. Sci.* **59**, 200–205 (2014).
49. Sioen, I., Lust, E., de Henauw, S., Moreno, L. A. & Jiménez-Pavón, D. Associations between body composition and bone health in children and adolescents: a systematic review. *Calcif. Tissue Int.* **99**, 557–577 (2016).
50. Mostoufi-Moab, S. et al. Adverse fat depots and marrow adiposity are associated with skeletal deficits and insulin resistance in long-term survivors of pediatric hematopoietic stem cell transplantation. *J. Bone Miner. Res.* **30**, 1657–1666 (2015).
51. Li, J., Kwong, D. L. W. & Chan, G. C. F. The effects of various irradiation doses on the growth and differentiation of marrow-derived human mesenchymal stromal cells. *Pediatr. Transplant.* **11**, 379–387 (2007).
52. Baxter-Jones, A. D. G., Faulkner, R. A., Forwood, M. R., Mirwald, R. L. & Bailey, D. A. Bone mineral accrual from 8 to 30 years of age: an estimation of peak bone mass. *J. Bone Min. Res.* **26**, 1729–1739 (2011).
53. Mogil, R. J. et al. Effect of low-magnitude, high-frequency mechanical stimulation on BMD among young childhood cancer survivors a randomized clinical trial. *JAMA Oncol.* **2**, 908–914 (2016).
54. Elnaggar, R. K. & Mohamed, R. R. Aqua-plyometric exercises: potential implications for bone mineral density, functional capacity, and quality of life in survivors of childhood acute lymphoblastic leukemia. *Semin. Oncol. Nurs.* **37**, 151225. https://doi.org/10.1016/j.soncn.2021.151225 (2021).
55. Dubnov-Raz, G. et al. Changes in fitness are associated with changes in body composition and bone health in children after cancer. *Acta Paediatr.* **104**, 1055–1061 (2015).
56. Petit, M. A. et al. Proximal femur bone geometry is appropriately adapted to lean mass in overweight children and adolescents. *Bone* **36**, 568–576 (2005).
57. Mostoufi-Moab, S. et al. Body composition abnormalities in long-term survivors of pediatric hematopoietic stem cell transplantation. *J. Pediatr.* **160**, 122–128 (2012).
58. Mostoufi-Moab, S. et al. Bone density and structure in long-term survivors of pediatric allogeneic hematopoietic stem cell transplantation. *J. Bone Miner. Res.* **27**, 760–769 (2012).
59. Mostoufi-Moab, S. & Halton, J. Bone morbidity in childhood leukemia: epidemiology, mechanisms, diagnosis, and treatment. *Curr. Osteoporos. Rep.* **12**, 300–312 (2014).
60. Shawwa, K. et al. Predictors of trabecular bone score in school children. *Osteoporos. Int.* **27**, 703–710 (2016).
61. Ubago-Guisado, E. et al. Longitudinal determinants of 12-month changes on bone health in adolescent male athletes. *Arch. Osteoporos.* **13**, 106. https://doi.org/10.1007/S11657-018-0519-4 (2018).
62. Ireland, A. et al. Upper limb muscle-bone asymmetries and bone adaptation in elite youth tennis players. *Med. Sci. Sports Exerc.* **45**, 1749–1758 (2013).

ACKNOWLEDGEMENTS

Herein, we would like to thank the disposal and consideration of all families involved in the investigation. The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Pediatric Research*. The corresponding author affirms that all authors have contributed significantly to the work.

AUTHOR CONTRIBUTIONS

A.M.-P., F.J.L.-C., E.U.-G., A.R.-S., J.J.G.-C., J.R.R. and L.G.-M. coordinated the study sites, including participant recruitment. A.M.-P., E.U.-G., A.R.-S., J.J.G.-C. and L.G.-M. wrote all the protocol versions, and obtained ethical approval and funding. L.G.-M. was the principal investigator. A.M.-P., F.J.L.-C., E.U.-G., A.R.-S., J.J.G.-C. and L.G.-M. were responsible for data collection, including clinical data. A.M.-P. conceptualised and designed the study with the support of E.U.-G., D.V. and L.G.-M. A.M.-P. drafted the initial manuscript and all co-authors were involved in the interpretation of data, revised the manuscript and approved the final manuscript as submitted.

FUNDING

This study has been partially supported by the Spanish Ministry of Science and Innovation (ref: PID2020-117302RA-I00 financiado por MCIN/ AEI /10.13039/501100011033), La Caixa Foundation (ref: LCF/BQ/PR19/11700007), the University

of Granada Plan Propio de Investigación 2021-Excellence actions: Unit of Excellence on Exercise, Nutrition and Health (UCEENS) and the CIBEROBN, Centro de Investigación Biomédica en Red (CB22/03/00058), Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación and Unión Europea – European Regional Development Fund. A.M.-P. is the recipient of a predoctoral fellowship (FPU20/05530) by the Spanish Ministry of Education, Culture and Sport. E.U.-G. is supported by the Maria Zambrano fellowship by the Ministerio de Universidades y la Unión Europea—NextGenerationEU.

COMPETING INTERESTS

The authors declare no competing interests.

CONSENT TO PARTICIPATE

All parents and participants provided the required consent and assent, respectively.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41390-023-02645-8.

Correspondence and requests for materials should be addressed to Esther Ubago-Guisado.