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Adaptation of Proximal Femur to Mechanical Loading in Young Adults: Standard vs. Localized Regions Evaluated by DXA

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Running Title: Adaptation of proximal femur to mechanical loading

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Abstract

Regions of the proximal femur with less adaptive protection by mechanical loading may be at increased risk of structural failure. Since the size and location of these regions diverge from those defined by the DXA manufacturers the purpose of this study was to compare areal bone mineral density (aBMD) of different regions of the proximal femur considering impact loads from physical activity (PA).

The participants were 134 young adults divided into two groups according to the impact of PA performed in the last 12 months: high-impact PA (HPA) and low-impact PA (LPA). The aBMD of the proximal femur was assessed by DXA at the standard femoral neck (FN), intertrochanter, and trochanter, and at specific locations of the superolateral femoral neck (SFN) and intertrochanteric regions (ITR). The Bone-specific Physical Activity Questionnaire was used to estimate the impact load of PA. Comparisons between groups were adjusted for body height and body lean mass. Interaction analysis between sex and PA groups were conducted with ANCOVA. Comparisons of aBMD between bone regions were analyzed separately for men and women with repeated measures ANCOVA. In the HPA group, men benefit more than women at all bone regions, except the aBMD at ITR. Analyses of repeated measures did not reveal any significant interaction effect between bone regions (standard vs. specific) and PA groups (low vs. high-impact). In conclusion, aBMD differences due to mechanical loading were more pronounced in men than in women; the magnitude of the aBMD differences as a result of different levels of PA was similar between standard and localized regions.

Keywords Bone density, BPAQ, Sex, Physical activity, Proximal femur, Superolateral neck

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Introduction

Bone fragility is one of the determinants of fractures occurring in the absence of trauma or as a result of a low trauma, typically following a fall from standing height or less. These fractures are due to a decreased resistance to loading forces, i.e., a decrease in bone strength (1, 2). Bone strength describes the whole integrity of the bone and involves the bone material properties (organic and inorganic components), cellular activity, and bone structural properties (micro- and macroarchitecture) (3). However, the inorganic composition, expressed as areal bone mineral density (aBMD, g/cm^2) and measured using dual-energy X-ray absorptiometry (DXA), is the main clinical criteria to evaluate the risk of fragility fractures.

According to the recommendations of the International Society for Clinical Densitometry, the assessment of bone fragility by DXA is conducted in the standard regions of the spine, femur, and radius namely in the lumbar spine, in the total proximal femur or femoral neck, and, in certain circumstances, in the 33% radial site (4). Recent evidence suggests, however, that assessment of bone fragility in other regions of the proximal femur may present a greater discrimination of fracture risk (5). These other regions are identified through computational anatomy using statistical parametric mapping techniques to compare 3D density values (obtained by quantitative computed tomography; QCT) between subjects with and without hip fractures. This approach allows to identify focal bone loss in ageing as a predictor of fracture (6-8) and consequently may contribute to a greater anatomical focus of anti-fracture interventions such as exercise or physical activity in the most vulnerable regions of the proximal femur.

Li et al. were the first to use this approach to identify proximal femoral tissue elements with the highest association with hip fracture (9). The authors showed that bone density differences were not uniformly distributed. The greatest differences were found in the superomedial quadrant of the femoral head, in the superolateral half of the femoral neck, and in the central region of the intertrochanter; bone mineral density measured in such regions discriminated hip fracture risk better than bone mineral density in standard anatomic regions (9). Using the same approach, other regions with bone mineral deficit have been identified in women with hip fracture, namely the inferomedial region of the femoral neck (10). However, this region, as opposed to the superolateral neck, appears to be relatively well preserved with mechanical load associated with the usual activities of daily living.

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These observations suggest that bone regions of the proximal femur at high risk of fracture may correspond to regions that are less mechanically stimulated during habitual load bearing. These regions are anatomical sites where tensile forces seem to predominate (lateral side) compared to compression forces that act on the medial side (11) (Figure 1). However the proximal femur appears to work principally in compression and not in bending-induced tension (12) due to the predominant physical activity in humans that is gait. These tensile forces are associated with more intense activities than gait (13).

Several studies have elucidated the importance of weight bearing physical activity and exercise in the material and structural properties of the growing skeleton in both sexes (14). These studies have not been conducted to elucidate whether the observed benefits occur in the most vulnerable regions of the proximal femur, particularly in those sites that have to withstand the forces generated from a lateral fall, the direction of the fall with the highest probability of fracture of the proximal femur (15).

Other studies exploring regional adaptation of the femoral neck to physical exercise have identified heterogeneous adaptation, with adaptation principally occurring at the inferior, anterior, and posterior regions but not at the superior region of the femoral neck in young adult females athletes from distinct sports (16) or with small differences in the superior region in older men who participated in a home-based impact exercise intervention (unilateral hopping) during 12 months (17). Given the heterogeneity of the effects of physical activity/exercise on the proximal femur, it is necessary to identify programs capable of strengthening the regions that most predispose to hip fracture (18).

The identification of vulnerable regions to fracture as well as the evaluation of the possibility of the exercise or physical activity to prevent this vulnerability is only possible using 3D images obtained by CT technology. However, the estimation of fracture risk will probably continue to be performed by DXA due to increased CT radiation in routine clinical practice. In this context, the purpose of this study was to compare the aBMD of different bone regions of interest in the proximal femur in young adults with different impact loads in this area of the skeleton, particularly aBMD of standard regions and those proposed by Li et al. (9). As described by Wolff’s law (19), the mechanisms that control bone modeling and remodeling should help to maintain bone mineral mass in regions that are highly stressed during

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habitual daily activity. Therefore, it is likely that people with a higher level of intensity in day-to-day activities will present greater differences in bone mineral density in the bone regions that are most exposed to tension forces, that is, in the localized regions proposed by Li et al. (9) compared to the standardized regions defined by DXA. This is an exploratory study to analyze the added value of specific regions in the evaluations of the proximal femur through DXA.

Figure 1

Material and Methods

Participants

The recruitment of participants was performed by direct contact, mailing, social networking, and a web site posting at the University of xxxx. Initially, 143 participants were recruited, of which nine participants were excluded because of problems related to completing the Bone-specific Physical Activity Questionnaire (BPAQ) (20). Finally, 134 young adults aged 20 to 35 years were allocated into two groups according to the impact of physical activity performed in the last 12 months having a median of 8.3 as the separation value: high-impact (HPA, n=68) and low-impact (LPA, n=65) groups. In the HPA group all participants presented current BPAQ scores between 10 and 154 while in the LPA group 62 participants had scores ≤1, one participant had a score of 3 and 2 participants a score of = 8. Each group was further subdivided according to sex. Therefore, four groups were established: 1) women with LPA (n=31) and HPA (n=25) and men with LPA (n=33) and HPA (n=45).

To be included in the study, all participants needed to be healthy, Caucasian, young adults (aged 18 to 35 years), not taking any medication affecting bone metabolism, and with no hip fracture in the past.

All the women were eumenorrheic with menstrual cycles between 21 and 35 days. Information on reproductive health was acquired through a questionnaire. Informed consent was obtained from each participant. The study design, protocol, and consent forms were prepared in accordance with the Helsinki Declaration of 1964 (revised in Fortaleza, 2013) and were reviewed and approved by the Ethics Committee of the xxxxxxxx.

Body size and composition

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Height was measured using a stadiometer to the nearest 0.1 cm (Seca 770, Hamburg, Germany). Then, the participants were weighed using a scale to the nearest 0.1 kg (Seca Alpha model 770, Hamburg, Germany); they had been in a fasting state for at least 4 h and were weighed without shoes and with minimal clothing. Body mass index was calculated as weight in kilograms divided by square height in meters. Total body fat mass (kg, %) and lean soft tissue (kg) were determined by DXA (QDR Explorer, version 13.3:3 Hologic, Waltham, MA, USA) with subjects fasted. All DXA scans were performed by the same technician and strictly standard protocols for positioning and analysis defined by the manufacturer were followed.

Bone measures

The aBMD of the proximal femur was assessed by DXA (QDR Explorer, version 13.3:3 Hologic, Waltham, MA, USA), by the same technician who also calibrated the device following the manufacturer's guidelines. After recording the aBMD results of the standard regions of interest defined by the manufacturer, namely the femoral neck, the intertrochanter, and the trochanter (Figure 2A), a manual analysis of each hip scan was performed to delimit the regions proposed by Li et al. (9), i.e., the superolateral neck and the intertrochanteric region. Although the femoral head was also proposed by Li et al. (9) it was not considered in the present study because of the overlap with the acetabulum.

To delimit the superolateral neck region, the inferomedial neck box line was displaced up toward the proximal femur axis to reach the midline, and the superolateral neck box line was moved to draw a box of 15x15 mm; this box was then positioned at the lower part of the femoral head (Fig. 2B). For the intertrochanteric region, the superolateral neck box line was moved up to reach the midline, and the inferomedial neck box line was moved to form a box with a size of 15x15 mm; the upper border of this box was placed in the mid-distance between the lower border of the neck and the lowest point of the hip axis length (Figure 2C). The coefficients of variation in measuring the aBMD of the different regions of interest were estimated from two measurements by repositioning and scanning 29 subjects and were less than 1.6% (femoral neck: 1.5%; intertrochanter: 1.3%; trochanter: 1.4%; superolateral neck: 1.6%: intertrochanteric region: 1.4%).

Figure 2

Physical activity

The BPAQ was developed by Weeks et al. (20) to estimate the mechanical loading impact associated with physical activity in healthy young adults. Methodological considerations have been previously published (11). Loading intensity, years of participation, and frequency were weighted using two approaches according to the osteogenic index developed by Turner and Robling (21). To calculate current BPAQ (cBPAQ), all activities practiced on a regular basis over the 12 months previous to testing were taken into account according to the following algorithm:

cBPAQ=(R+0.2*R (n-1))*a.

where R is the effective load stimuli derived from ground reaction forces testing, n is the weekly frequency of participation in sports activity, and a is the weighting factor for age; given the age of the sample was used a weighting factor of 1.1.

For the past BPAQ (pBPAQ, birth to 12 months prior to testing), the algorithm was estimated as follows:

pBPAQ=R*y*a

where y is the number of years of participation in sports activity and a is a weighting factor for the age of sport participation (0.25 for ages up to15 years and 0.10 for higher ages).

Finally, total BPAQ (tBPAQ) was calculated as the sum of pBPAQ and cBPAQ. Equivalences of mechanical loading intensity were applied to sports that were not included in the original database; for instance, handball was considered equivalent to basketball, and rhythmic gymnastics was considered comparable to dance (22). The conversion of the raw BPAQ data into an individual score that reflects total bone-relevant sports activity history was done through the BPAQ online calculator (www.fithdysign.com/BPAQ/).

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences version 22.0 for Windows (SPSS Inc., Chicago, IL, USA), and significance was set at $P<0.05$. Mean, standard deviation (SD), and standard error (SE) are given as descriptive statistics. Kolmogorov-Smirnov tests were performed showing a normal distribution pattern of quantitative variables. Univariate analyses of variance were used to examine differences among groups for age, body composition, and physical activity variables. Analyses of covariance controlling for body height and lean mass were

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used to test for main effects and interaction between sex and impact physical activity on aBMD of bone regions of interest. Repeated measures ANCOVA controlling also for body height and body lean mass were performed to test for interaction between bone sites (std-femoral neck vs. Li-superolateral neck region; std-inter-trochanter vs. Li-intertrochanteric region) and physical activity groups (low vs. high-impact) on aBMD, separately for both sexes.

Results

Participant descriptive characteristics are provided in Table 1. All groups of participants revealed similar age and tBPAQ. HPA men were heavier and taller and presented more lean and less fat masses than the other groups (all $P<0.05$), whereas LPA men were also heavier and taller, with more lean and less fat masses than LPA women. With the exception of cBPAQ, no differences were found between LPA and HPA women regarding age and body composition.

Table 1

Main and interaction effects of sex and physical activity on aBMD of DXA standard bone regions and bone regions proposed by Li et al. (9) adjusted for body height and body lean mass are depicted in Table 2. The interaction between sex and physical activity impact groups was significant for all bone regions ($P<0.05$), with the exception of intertrochanteric region (as described by Li et al. (9). At important skeletal sites in the HPA group, men benefit more than women, as illustrated in Figure 3. Men showed higher aBMD than women in two out of five skeletal sites. The femoral neck at both locations were the variables that showed differences between the sexes. In turn these same variables were those that did not show differences between the LPA and HPA groups.

Table 2

Figure 3

Analyses of repeated measures controlling for body height and body lean mass were performed to test for interaction between bone regions (std-femoral neck vs. Li-superolateral neck aBMD; std-inter-trochanter vs. Li-intertrochanteric region) and physical activity groups (low vs. high-impact) on aBMD, separately for both sexes (Figure 4). It was not observed any interaction effect.

Figure 4

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Discussion

The aim of this study was to analyze the adaptation of different regions of the proximal femur to impact loading from physical activity in young adults. To this end, we compared aBMD differences of several (standard and new) bone regions of interest in the proximal femur between men and women with different mechanical intensity levels of physical activity. All bone regions showed higher aBMD in men and women from the HPA groups than their LPA counterparts, and the most pronounced differences were between men than between women. In women, specific regions revealed greater aBMD differences than the standard regions (10.1 - 11.4% vs. 5.5 - 6.3% aBMD diff between LPA and HPA groups, respectively), however there were no significant combined effects (bone region x physical activity group).

Li et al. (9) identified critical regions inside the proximal femur through a voxel-by-voxel statistical comparison (statistical parametric mapping) between patients with fractures and controls using 3D images obtained from QCT. The critical regions identified by these authors were localized superiorly and internally in the femoral head, superiorly in the femoral neck, and inside the intertrochanteric region. Using DXA, which is a rapid, safe, and accessible technique for clinicians and researchers (23), our results were not able to show that the critical regions (foci of bone loss) suggested by Li et al. (9) coincide with the highest aBMD differences associated with the mechanical intensity of physical activity. These results do not agree with the initial assumption of the present study that the most relevant regions have smaller size (localized) and are placed where tensile forces from mechanical loading are greater. According to these observations, DXA evaluation of proximal femur regions proposed by Li et al. (9) does not seem to be an added value to identify or monitor bone weakness/strength, despite the evidence that standard DXA examinations may not provide an accurate representation of highly localized adaptations caused by mechanical stimulus (24-25).

The inferomedial neck is another region of the proximal femur that is pointed out as critical for the predisposition to fracture, particularly for trochanteric fracture (26). Older women with hip fracture seem to present a deficit of cortical BMD not only at the upper but also at the lower compartment of the femoral neck, a primary load-bearing region (10, 26). The inferomedial neck was not included in the present study because it was intended to compare the magnitude of aBMD differences between adults with different physical activity history relevant to the proximal femur. This

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specific region appears to show minor differences not only between younger and older people (10) but also between more and less active people although aBMD is always higher in the inferomedial than in the superolateral neck (22).

Whether there is a sex-dependent bone response to physical activity is currently an open research question. Although animal studies (25) and some studies with tennis players (27) suggest that bone tissue is less responsive to loading in females than in males because of estrogenic effects (28), human studies in general suggest similar skeletal response in both sexes (29), or were unable to elucidate sex differences (14). However, have been described a lower response to physical activity in girls than in boys at ages where estrogen production is inhibited or is low (30-32). Moreover, the effect of physical activity on the proximal femur does not seem to be homogeneous throughout all bone regions in girls (33). Cardadeiro et al. (33) observed that more active pre- and peripubertal girls had greater aBMD in the trochanter and intertrochanter than in the femoral neck regions, whereas more active boys did not demonstrate any difference between the proximal femur regions, i.e., all regions seemed to benefit equally. However, differences between boys and girls in bone mass distribution among the proximal femur regions may be better explained by bone geometry and not by differences in responses to sex-specific physical activity (14, 34).

Focusing on sex and physical activity interactions, the current study revealed that in general, men benefit more than women from physical activity with high-impact loading. While in the LPA groups no differences of aBMD were observed in any bone region between men and women, in the HPA groups these differences were evidenced between sexes. Despite the fact that men presented similar scores to women in the cBPAQ, it seems the male skeleton is more responsive to mechanical loading or, for the same amount of high-impact physical activity, the mechanical load is greater in men than in women probably because of a greater muscle mass in action. The bone was subjected to greater loads in the HPA than in the LPA group as the bones in the former group are associated with higher production of muscle forces (peak vertical ground reaction forces x rates of force application) (20), particularly when knee and hip extension occurs (13, 24). However, the study did not capture a more localized response arising from high-impact physical activity to strengthen the proximal femur to reduce hip fragility, particularly at the superolateral aspect of the femoral neck, a relatively unstimulated region by routine mechanical load (9, 35-38).

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The present study has some limitations. As with all cross-sectional studies, this work does not permit the inference of causal relationships. Categorization of the participants by mechanical loading intensity was based on a physical activity questionnaire that generates scores according to load magnitude and loading rate (BPAQ) (20). Despite not being an objective evaluation, this approach allowed us to collect information from an extended period (12 months and lifetime), which otherwise would not be possible. Correlations adjusted for body height and lean mass between the bone variables and physical activity were superior with the cBPAQ ($r = 0.205$-0.344 in women, $r = 0.345$-0.499 in men) than with the tBPAQ ($r = 0.197$-0.267 in women, $r=0.060$-0.095 in men) particularly in males (data not shown), and therefore, the division of participants by groups was performed according to the cBPAQ. Greater associations of bone variables with cBPAQ than with tBPAQ may be due to differences between the patterns of bone-relevant physical activity in adulthood and youth and differences in maturation between sexes not equated in the formula of the tBPAQ (20). Higher activity according to the exposure to the mechanical load without taking into account either the type or direction of force may however not be sufficient to capture potential differences between specific bone regions induced by specific mechanical stimuli (18). Yet, the score obtained by each participant in physical activity, is representative not only of the various types of physical activities practiced throughout life (tBPAQ) or in the last 12 months (cBPAQ) but also of the duration of participation in each of the physical activities, and the phase of the life cycle in which physical activities were practiced. In this sense, the score expresses the osteogenic potential of physical activity history according to the mentioned parameters.

Another limitation of the study was the definition of the size and location of the regions identified in 3D (QCT) in 2D images (DXA) and, consequently, the correspondence between bone regions of interest obtained by the two types of equipment. In this study, the new DXA regions of interest were delimited using box lines and sizes of the DXA analysis software and with reference to anatomical markers. The use of anatomical markers (proximal femur axis, lower part of femoral head, lower border of the neck and lowest point of hip axis length) ensured a standardized location for the new DXA regions of interest in all participants. The size of these regions (15x15 mm) may, however, represent a variable portion of bone, overestimating the aBMD in those with larger bones. This methodological limitation

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happens for all aBMDs assessed by DXA and usually is corrected having body height as covariate, as was done in this study. The absence of an interaction between bone regions x physical activity groups may also be due to the lack of sensitivity of DXA to assess bone density. The assessment of aBMD by DXA does not translate into a real bone density because it is a technology that projects in 2D a 3D bone structure. Unlike DXA, QCT measures bone density using 3D and thus is a more accurate method.

In conclusion, the aBMD differences due to mechanical loading were more pronounced in men than in women; the magnitude of the aBMD differences as a result of different levels of physical activity was similar between the superolateral femoral neck and intertrochanteric regions identified by Li et al. (9) and the standard regions defined by the DXA manufacturers.

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Authors Contributions

xx conceived the work, analyzed and interpreted the data, and elaborated and revised the manuscript. yy and cc contributed to the acquisition and analysis of the data and to the elaboration of the manuscript. bbbb and nnn analyzed and interpreted data for the work and revised statistical content. All authors have made substantial contributions to the work and approved it for publication.

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Conflict of interest

All authors have no conflicts of interest.

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Figure 1. Orientation of the trabecular structure (compressive and tensile trabecular groups and greater trochanter group) in accordance with mechanical loading (body weight) applied to the proximal femur, adapted from Geraldes et al. (13).

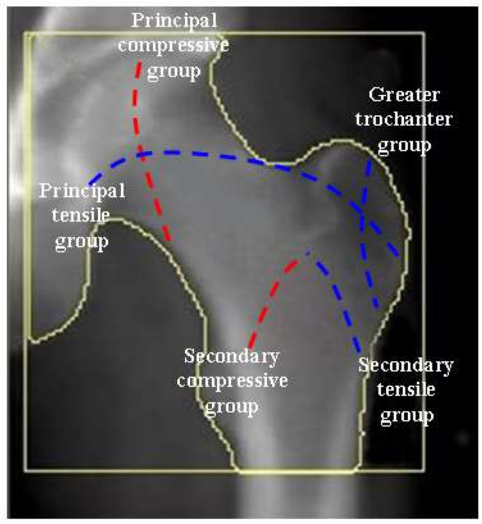

Figure 2. Bone regions of interest: (A) DXA standard regions: 1, femoral neck; 2, trochanter; 3, intertrochanter; (B-C) regions proposed by Li el al (9): B, superolateral femoral neck; C intertrochanteric region.

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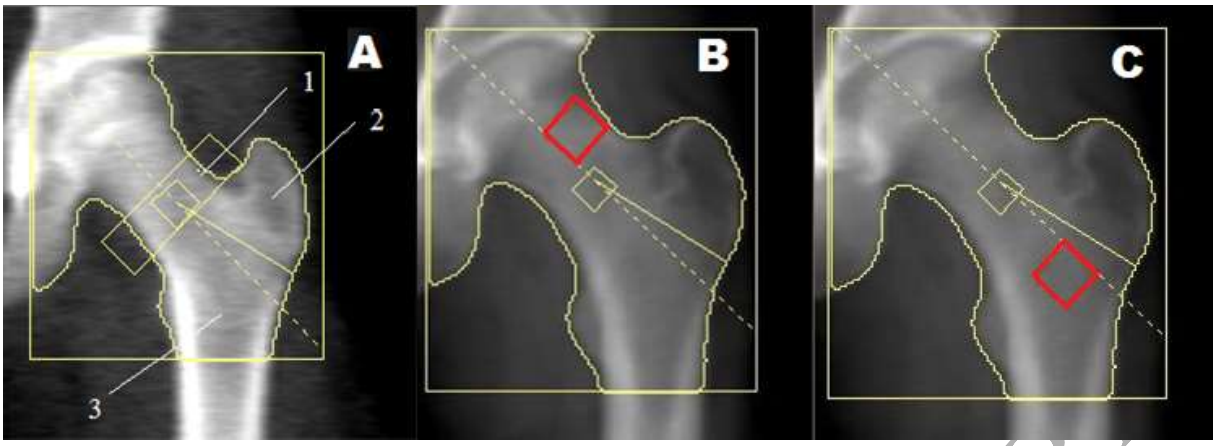

Figure 3. Interaction effects of sex and impact physical activity on aBMD of DXA standard bone regions and bone regions proposed by Li et al. (9) adjusted for body height and body lean mass.

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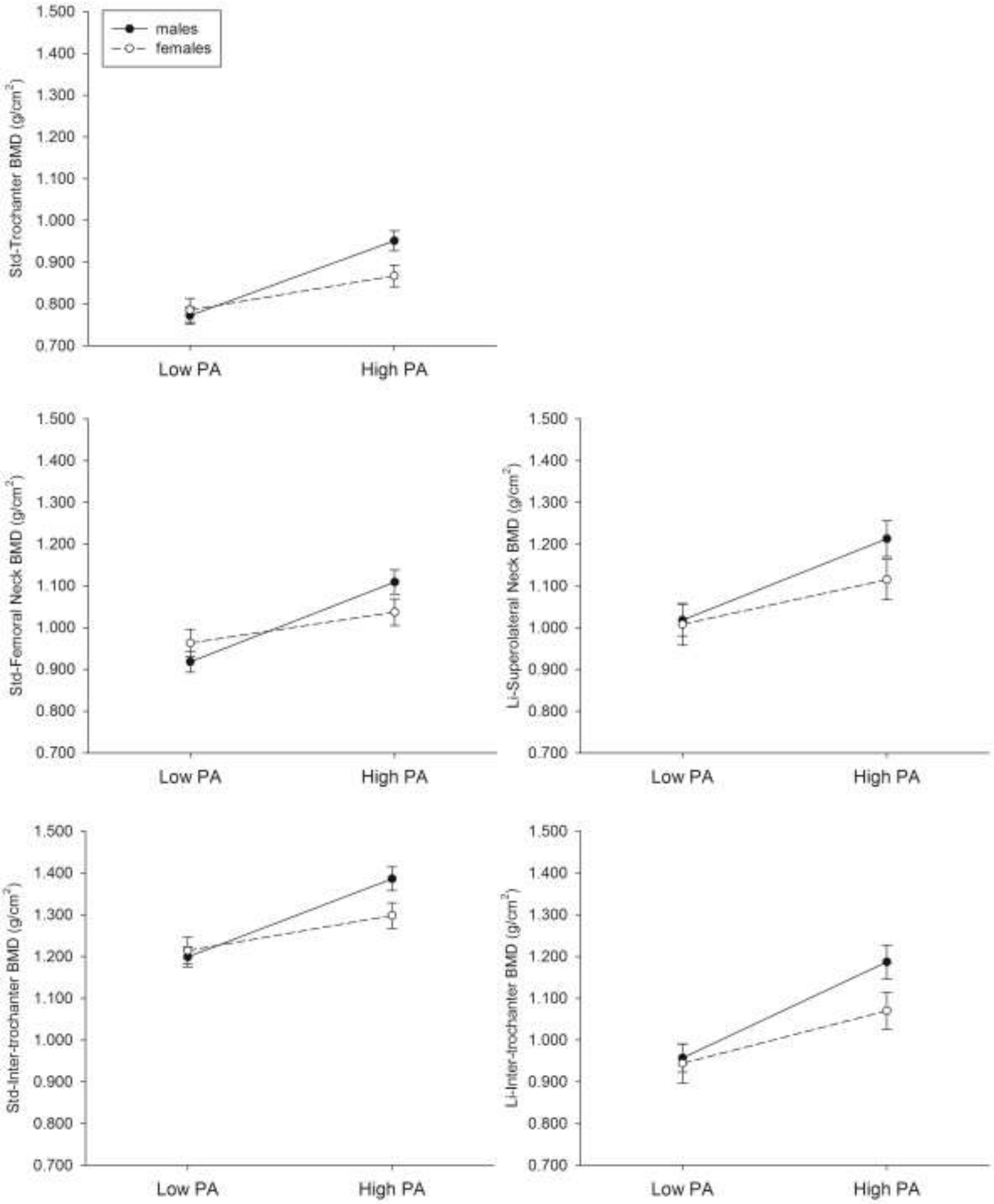

Figure 4. Interaction effects of bone region and impact physical activity on aBMD adjusted for body height and body lean mass.

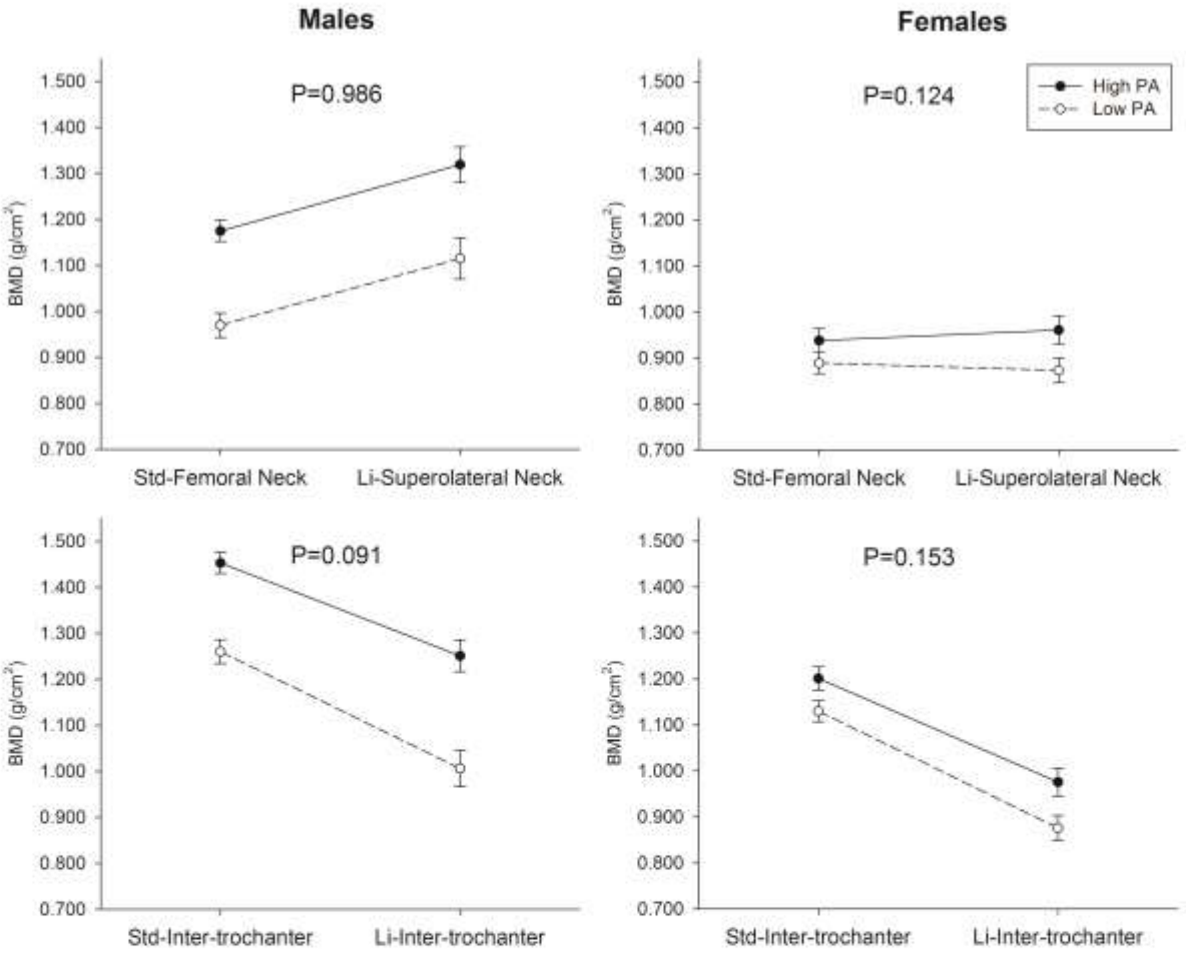

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Table 1. Descriptive characteristics of the participants (Mean±SD).

	Low PA	High PA	*P-Values*
Age (yrs)			
Females	24.0±3.6	23.0±3.6	1.000
Males	24.0±3.1	22.1±4.8	0.174
P-value F vs. M	1.000	1.000	
Body mass (Kg)			
Females	58.3±8.4	62.1±9.7	1.000
Males	70.4±8.2	77.0±14.7	0.058
P-value F vs. M	<0.001	<0.001	
Body height (cm)			
Females	162.2±5.3	165.4±6.6	0.328
Males	174.1±6.6	177.9±5.9	0.046
P-value F vs. M	<0.001	<0.001	
BMI (Kg/m²)			
Females	22.2±3.3	22.6±2.6	1.000
Males	23.2±2.5	24.3±4.0	<0.001

P-value F vs. M	0.460	<0.001	
Body Fat Mass (Kg)			
Females	16.2±6.0	15.9±5.7	1.000
Males	12.3±6.4	10.7±6.0	1.000
P-value F vs. M	0.060	0.005	
Body Fat Mass (%)			
Females	27.4±6.6	25.3±6.2	1.000
Males	17.2±6.9	13.4±4.5	0.038
P-value F vs. M	<0.001	<0.001	
Lean Soft Tissue (Kg)			
Females	39.8±4.9	43.5±6.0	0.317
Males	55.1±6.3	66.4±9.1	<0.001
P-value F vs. M	<0.001	<0.001	
Current BPAQ			
Females	0.1±0.2	19.9±10.9	<0.001
Males	0.7±1.9	17.8±7.9	<0.001
P-value F vs. M	1.000	0.158	
Total BPAQ			
Females	13.9±24.0	25.7±18.8	0.481
Males	15.2±38.1	20.4±10.1	1.000
P-value F vs. M	1.000	1.000	

PA, physical activity; BMI, body mass index; BPAQ, bone-specific physical activity questionnaire

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Table 2. Main and interaction effects of sex and physical activity on aBMD (g/cm^2) of DXA standard bone regions and bone regions proposed by Li et al. (9) adjusted for body height and body lean mass (Mean±SE).

	Sex			Physical Activity			Sex x PA
	Females	Males	p	Low impact	High impact	p	p
Std-Trochanter BMD	0.826±0.022	0.862±0.017	0.288	0.779±0.016	0.910±0.015	<0.001	0.021

Std- FN BMD	1.001±0.026	1.012±0.020	0.001	0.941±0.019	1.072±0.018	0.164	0.021
Std-Inter-trochanter BMD	1.257±0.025	1.292±0.020	0.345	1.207±0.018	1.342±0.017	<0.001	0.037
Li-Superolateral FN BMD	1.063±0.040	1.113±0.031	0.006	1.014±0.029	1.163±0.027	0.100	0.011
Li-Intertrochanteric BMD	1.009±0.050	1.071±0.028	0.237	0.951±0.026	1.128±0.024	<0.001	0.136

PA. physical activity; Std. standard; BMD. bone mineral density; FN. femoral neck

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