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Bone marrow fat fraction assessment in regard to physical activity: KORA FF4–3-T MR imaging in a population-based cohort

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Abstract

Objectives To establish the effect of different degrees and kinds of physical activity on bone marrow fat (BMAT) content at different anatomical locations in a population-based cohort study undergoing whole-body MR imaging.

Methods Subjects of the KORA FF4 study without known cardiovascular disease underwent BMAT fat fraction (FF) quantification in L1 and L2 vertebrae and femoral heads/necks (hip) via a 2-point T1-weighted VIBE Dixon sequence. BMAT-FF was calculated as mean value (fat image) divided by mean value (fat + water image). Physical activity was determined by self-assessment questionnaire regarding time spent exercising, non-exercise walking, non-exercise cycling, and job-related physical activity.

Results A total of 385 subjects (96% of 400 available; 56 ± 9.1 years; 58% male) were included in the analysis. Exercise was distributed quite evenly (29% > 2 h/week; 31% ~ 1 h/week (regularly); 15% ~ 1 h/week (irregularly); 26% no physical activity). BMAT-FF was 52.6 ± 10.2% in L1, 56.2 ± 10.3% in L2, 87.4 ± 5.9% in the right hip, and 87.2 ± 5.9% in the left hip (all $p < 0.001$). Correlation of BMAT-FF between spine and hip was only moderate (r 0.42 to 0.46). Spinal BMAT-FF, but not hip BMAT-FF, was inversely associated with exercise > 2 h/week ($p \leq 0.02$ vs. $p \geq 0.35$, respectively). These associations remained significant after adjusting for age, gender, waist circumference, and glucose tolerance. No coherent association was found between BMAT-FF and physical activity in the less active groups.

Conclusions In our study, exercise was inversely correlated with vertebral BMAT-FF, but not hip BMAT-FF, when exercising for more than 2 h per week. Physical activity seems to affect the spine at least preferentially compared to the hip.

Key Points

- *In our population-based cohort, at least 2 h of physical activity per week were required to show lower levels of bone marrow adipose tissue fat fraction in MRI.*
- *Physical activity seems to affect bone marrow adipose tissue at least preferentially at the spine in contrast to the proximal femur.*

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Keywords Physical activity · Bone marrow · Adipose tissue · Magnetic resonance imaging · Fat fraction

Abbreviations

BMAT	Bone marrow adipose tissue
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
FF	Fat fraction
L1	Lumbar vertebra 1
L2	Lumbar vertebra 2
LH	Left hip = left proximal femur
PDFF	Proton density fat fraction
RH	Right hip = right proximal femur
ROI	Region of interest
SD	Standard deviation
WC	Waist circumference

Introduction

Bone marrow adipose tissue (BMAT) has become an area of intense research, reflected by the formation of the International Bone Marrow Adiposity Society (http://bma-society.org/) in 2017. The increasing interest of this unique fat phenotype [1–3] and endocrine organ [4] arises from a yet not fully understood association with something known as bone health incorporating osteoporotic changes, fracture risk, impaired bone formation, hematopoiesis, or maybe even effects on tumor progression [3–7]. It is influenced, among others, by age [8–11], gender [8, 12], and nutritional status, e.g., anorexia nervosa or obesity, both showing increased BMAT [13–15]. Diabetes seems to possibly have a complex influence [16].

Physical activity is a well-known factor influencing body weight and BMI [17–19] leading to a reduction on total, trunk, abdominal, visceral, and/or subcutaneous adipose tissue [20–27]. This has been shown for many kinds of physical activities [20–27], of note including energy consuming disciplines like cycling and swimming [20–22, 26, 27]. The effects of physical activity, or the opposite, inactivity or simulated weightlessness, on BMAT are less well understood. They have been mostly studied in animal models, preferentially on the lower extremity [28–34], and to a lesser extent on humans, usually on the spine [35–37] or lower extremities [38–40]. However, those studies did not look at both sites simultaneously. Investigation on humans has, to our knowledge, so far been restricted to relatively special settings. Trudel et al, e.g., looked at the effects of physical activity (resistive exercises) on BMAT in simulated zero-gravity via a 60-day head-down tilt bed rest which showed that exercise can mitigate the accumulation of BMAT in this weightlessness/immobilization experiment [35]. Belavy et al looked at a young athletic population which showed that some athletic activities (running, but not cycling) where associated with reduced spinal BMAT as measured by a 2-point Dixon MRI sequence [37]. Rantalainen et al showed similar results in a high mechanical impact subgroup of competitive female athletes which showed increased CT-measured mid-tibial bone marrow density as an estimate of inversely correlated bone marrow fat [39].

The purpose of this study was to determine how physical activity is associated with BMAT in an average non-athletic population, and to find the threshold of physical activity at which differences in BMAT-FF can be expected ranging from everyday activities to exercise.

Secondary aim was to compare BMAT-FF at the lower extremities and the spine, specifically the proximal femur ("hip"), which contains a mixture of cancellous bone, red and yellow marrow similar to vertebral bodies in adults.

Materials and methods

Study design and population

The 400 subjects of the KORA FF4 follow-up sub-study, recruited from the general population as a case-control study with a stratified selection of subjects without diabetes, with prediabetes or with diabetes, were analyzed for this study. Exclusion criteria included a history of cardiovascular disease, as described before [41, 42], and additionally of possible bone marrow cancer (Appendix E1).

Demographics and physical activity

Subjects were re-examined between 2013 and 2014 and along with weight, height, and waist circumference (WC), data was collected on physical activity via standardized questionnaires:

- Exercise: "How often do you exercise/workout?"—≥ 2 h per week, regularly; ~ 1 h per week, regularly; ~ 1 h per week, irregularly; no or nearly no workout. Initial division into summer and winter exercise was combined into one variable as described before [43].
- Non-exercise walking: "How long do you usually walk on a work day? (e.g., going for a walk, commuting, shopping)"—< 0.25 h; 0.25–0.5 h; 0.5–1 h; > 1 h.
- Non-exercise cycling: "How long do you usually ride a bicycle on a work day? (e.g., commuting, shopping)"—< 0.25 h; 0.25–0.5 h; 0.5–1 h; > 1 h.
- Non-exercise activity at work: "How would you describe your job/main work?"—no relevant physical labor; light

physical labor; moderate physical labor; heavy physical labor.

Magnetic resonance imaging

Whole-body imaging on a 3 T Magnetom Skyra (Siemens AG), as described previously [42], was performed within 3 months after the study center visit. Of this protocol, a coronally acquired 2-point Dixon T1-weighted VIBE CAIPIRINHA sequence (TR 4.06 ms; TE 1.26 ms, 2.49 ms; flip angle 4°; slice thickness 1.7 mm) covering the entire torso was selected to determine BMAT-FF from water and fat selective images which were automatically calculated by the manufacturer's software.

MR-based BMAT measurements

Image analysis was performed in blinded fashion by independent readers on dedicated software (OsiriX 7.0, Pixmeo SARL).

BMAT at vertebrae L1 and L2

BMAT-FF at L1 and L2 was measured in a single coronal image in the middle of the anterior-posterior diameter of the vertebral body, where all bone marrow including cancellous bone, but no cortical bone, was manually delineated on the fat image and copied to the water image (Fig. 1, upper row). Mean intensity values were derived.

BMAT at the right and left proximal femur

BMAT-FF at the proximal femurs were measured similarly in the single coronal slice which covered the largest area of the femoral neck. Again, all cancellous bone, but no cortical bone, was included (Fig. 1, lower row).

Post-processing of MR measurements

Estimates of BMAT-FF were calculated as before [36, 37, 44]:

$$estimate\ of\ \ BMAT\ fat\ fraction\ (in\%) = \frac{mean\ intensity_{fat\ image}}{mean\ intensity_{fat\ image} + mean\ intensity_{water\ image}}$$

They were set to missing in case of significant artifacts, incomplete coverage, significant degenerative disease, or hemangioma which made bone marrow assessment inadequate.

Intra- and inter-reader reproducibility

For intra-reader reproducibility, measurements were performed a second time in 30 subjects after 2 weeks. For inter-reader reproducibility, a random sample of 30 MR cases was read by a blinded second reader.

Statistical analysis

Subject demographics, physical activity, and MR-based measures of BMAT-FF are presented as means and standard deviations (SD) for continuous variables and counts and percentages for categorical variables, if not otherwise specified. Differences in characteristics between men and women were evaluated by *t* test or chi^2 test. Details regarding the intra- and inter-reader reproducibility analysis and model fitting are detailed in online Appendix E2.

A two-sided p value of < 0.05 was considered to indicate statistical significance. All analyses were conducted with Stata 14.1 (Stata Corporation).

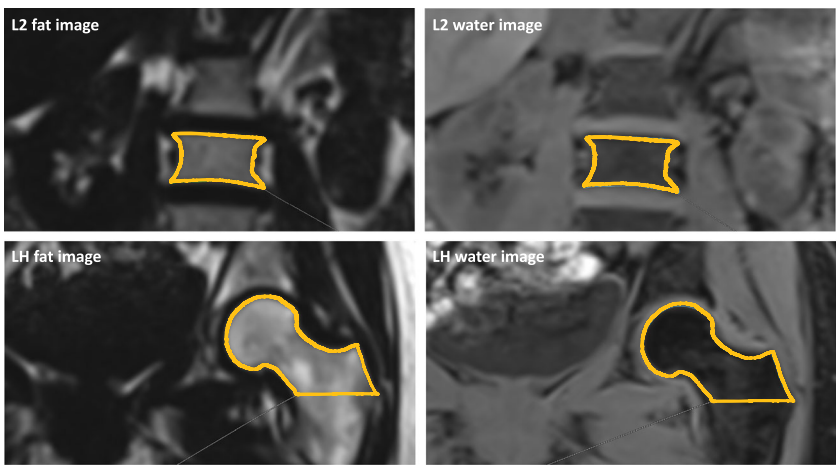

Fig. 1 BMAT-FF measurement in a coronally acquired 2-point Dixon vibe sequence. ROI manually drawn in the fat selective images and copied to the water selective images, exemplary at the L2 vertebra and the left hip (LH); in the latter, the inferior tip of the greater trochanter defines the lower boundary

Results

The population-based cohort consisted of middle aged (56 ± 9.1 years), Caucasian subjects with an average BMI of 28.5 kg/m^2 for male and 27.6 kg/m^2 for female. Male gender was slightly more frequent (58 vs. 42%; Table 1). Given the study design, 25% of subjects had prediabetes, 14% had diabetes. 28.6% performed exercise of 2 h regularly or more per week, with a similar male/female distribution. A similar percentage reported no or nearly no exercise (Table 1).

Of a total of 400 subjects, 1 subject was excluded because of possible bone marrow cancer by history, 14 subjects because of artifacts affecting all or the most important measurements. Measurement of L1-BMAT-FF, L2-BMAT-FF, RH-BMAT-FF, and LH-BMAT-FF were feasible in 96%, 95%, 55%, and 56%, respectively (Table 1). Missing hip measurements were mostly due to insufficient coverage.

Reproducibility

Intra-reader agreement was excellent for L1-BMAT-FF, L2-BMAT-FF, LH-BMAT-FF, and RH-BMAT-FF with an ICC of 0.98, 0.98, 0.91, and 0.96, respectively, with a relative difference of the mean of the two measurements below or equal to 2.1% (Supplementary Appendix Fig. 1). Inter-reader agreement was also excellent with an ICC of 0.90, 0.97, 0.92, and 0.96, respectively, with a relative difference of the mean below or equal to 6.3% (Supplementary Appendix Fig. 2).

Table 1 Characteristics of the entire study cohort

	All	Male	Female	*p* value
N	385	222	163	
Age (years)	56.2 (± 9.1)	56.0 (± 9.3)	56.3 (± 9.0)	0.73
BMI (kg/m^2)	28.1 (± 4.9)	28.5 (± 4.4)	27.6 (± 5.4)	0.06
WC (cm)	98.7 (± 14.4)	103.7 (± 12.4)	92.0 (±14.2)	< 0.001
Glucose tolerance				0.003
Normal glucose tolerance	235 (61.0%)	120 (54.1%)	115 (70.6%)	
Prediabetes	97 (25.2%)	63 (28.4%)	34 (20.9%)	
Diabetes	53 (13.8%)	39 (17.6%)	14 (8.6%)	
Exercise				0.06
≥ 2 h per week, regularly	110 (28.6%)	64 (28.8%)	46 (28.2%)	
~ 1 h per week, regularly	118 (30.7%)	58 (26.1%)	60 (36.8%)	
~ 1 h per week, unregularly	56 (14.6%)	32 (14.4%)	24 (14.7%)	
No or nearly no exercise	101 (26.2%)	68 (30.6%)	33 (20.3%)	
Job-related physical activity				< 0.001
Heavy physical labor	14 (3.6%)	9 (4.1%)	5 (3.1%)	
Moderate physical labor	98 (25.5%)	45 (20.3%)	53 (32.5%)	
Light physical labor	121 (31.4%)	61 (27.5%)	60 (36.8%)	
No relevant physical labor	152 (39.5%)	107 (48.2%)	45 (27.6%)	
Non-exercise walking				0.89
> 1 h	161 (41.8%)	92 (41.4%)	69 (42.3%)	
0.5–1 h	124 (32.2%)	70 (31.5%)	54 (33.1%)	
0.25–0.5 h	72 (18.7%)	42 (18.9%)	30 (18.4%)	
< 0.25 h	28 (7.3%)	18 (8.1%)	10 (6.1%)	
Non-exercise cycling				0.47
> 1 h	47 (12.2%)	27 (12.2%)	20 (12.3%)	
0.5–1 h	68 (17.7%)	35 (15.8%)	33 (20.3%)	
0.25–0.5 h	52 (13.5%)	35 (15.8%)	17 (10.4%)	
< 0.25 h	81 (21.0%)	44 (19.8%)	37 (22.7%)	
BMAT-FF				
BMAT-FF, L1 (%), available in *n* = 385	52.6 (± 10.2)	52.6 (± 9.5)	52.7 (± 11.1)	0.89
BMAT-FF, L2 (%), available in *n* = 380	56.2 (± 10.3)	56.3 (± 9.4)	55.9 (± 11.5)	0.73
BMAT-FF, right hip (%), available in *n* = 216	87.4 (± 5.9)	89.6 (±3.3)	86.1 (± 6.7)	< 0.001
BMAT-FF, left hip (%), available in *n* = 219	87.2 (± 5.9)	90.0 (± 3.5)	85.6 (± 6.4)	< 0.001

BMAT-FF bone marrow adipose tissue fat fraction, *BMI* body mass index, *WC* waist circumference

Correlation between different BMAT-FF measurements

Mean BMAT-FF ranged from 52.6 to 90% depending on location and gender (Table 1). Fat content in the hip was always higher than in the vertebrae. There was a high correlation between L1 and L2 and right and left hip BMAT-FF measurements ($r = 0.93$ and 0.95, respectively; all $p < 0.001$; Appendix E3, Fig. 2), but a much lower correlation between spine and hip measurements ($r = 0.42$–0.46; Appendix E3, Fig. 2).

Differences in BMAT-FF between age, gender, BMI, WC, and glucose tolerance

BMAT-FF increased with age in all positions. Age showed stronger association with spinal BMAT-FF ($\beta = 0.53$ and 0.57) than with hip BMAT-FF ($\beta = 0.10$ and 0.18; all $p \leq 0.001$; Table 2). In contrast, BMAT-FF was significantly affected by gender at the hip ($\beta = 3.58$ and 4.37, all $p < 0.001$) but not at the spine (all $p \geq 0.73$). Of the obesity parameters, BMI did not show any significant association with spinal BMAT-FF (all

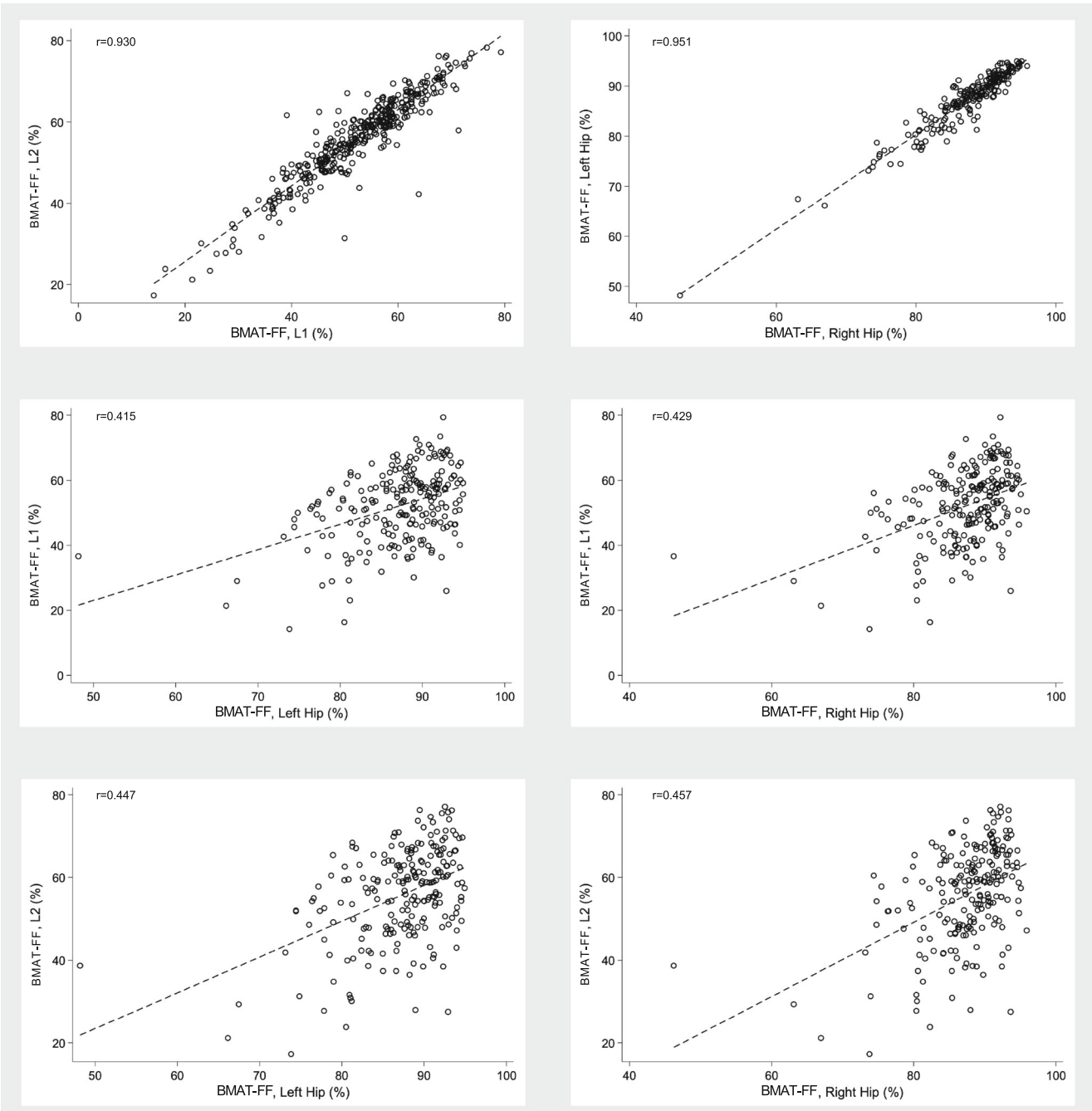

Fig. 2 Scatter plots of the correlation between different BMAT-FF measurements. Top row: spine vs. spine and hip vs. hip. Bottom rows: spine vs. hip. All $p < 0.001$

Table 2 Unadjusted association of BMAT-FF measurements with age, gender, BMI, WC, and diabetic status

	BMAT-FF, L1		BMAT-FF, L2		BMAT-FF, RH		BMAT-FF, LH	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Age	0.53 (0.43; 0.63)	< 0.001	0.57 (0.47; 0.67)	< 0.001	0.15 (0.07; 0.24)	0.001	0.18 (0.10; 0.27)	< 0.001
Male gender	−0.16 (−2.23; 1.92)	0.88	0.37 (−1.74; 2.49)	0.73	3.58 (2.01; 5.15)	< 0.001	4.35 (2.81; 5.90)	< 0.001
BMI	0.18 (−0.02; 0.39)	0.08	0.16 (−0.06; 0.37)	0.16	− 0.19 (− 0.35; − 0.02)	0.03	− 0.19 (− 0.35; − 0.03)	0.02
WC	0.1 (0.03; 0.17)	0.004	0.1 (0.03; 0.17)	0.008	− 0.02 (− 0.08; 0.03)	0.42	− 0.02 (− 0.08; 0.04)	0.47
Diabetic status*								
Prediabetes	2.24 (−0.15; 4.63)	0.07	2.68 (0.23; 5.13)	0.03	− 1.20 (− 3.27; 0.87)	0.25	− 1.61 (− 3.63; 0.41)	0.12
Diabetes	5.88 (2.88; 8.88)	< 0.001	5.60 (2.53; 8.66)	< 0.001	1.43 (− 1.00; 3.85)	0.25	1.36 (− 1.00; 3.73)	0.26

BMAT-FF bone marrow adipose tissue fat fraction (%), *BMI* body mass index (kg/m^2), *WC* waist circumference (cm)

*normal glucose tolerance serves as the reference.

L1: vertebral body L1. L2: vertebral body L2. RH: right hip. LH: left hip

$p \geq 0.08$) but with hip BMAT-FF (all $p \leq 0.03$); in contrast, WC was associated with spinal BMAT-FF (all $p \leq 0.008$) but not with hip BMAT-FF (all $p \geq 0.42$; Table 2). Similar, spinal but not hip BMAT-FF was different between normal glucose tolerance and diabetes (Table 2); thus, spinal BMAT-FF increased stepwise across normal, prediabetes, and diabetes.

Correlation of BMAT-FF with exercise

Irrespective of significance, BMAT-FF measurements were lower in all exercise groups in the spine and hips compared to our reference group; however, this difference was much smaller in the hip than in the spine (Table 3). Statistical significance, however, was only reached in the most active exercise group ("≥ 2h per week, regularly") which showed a 3.94% and 3.51% lower BMAT-FF in L1 and L2, respectively, compared to the reference group ("no or nearly no exercise"; Table 3). Hip BMAT-FF did not show a significant association with exercise (all $p > 0.23$). In multivariable regression analysis adjusting for age, gender, WC, and diabetic status, spinal BMAT-FF in the highest exercise group remained significantly lower compared to control, comparable to univariate analysis (Table 4, and Appendix E3). Again, there was no significantly lower BMAT-FF in the hip in multivariable analysis (Table 5).

Correlation of BMAT-FF with non-exercise walking, cycling, and job-related physical activity

In the non-exercise walking group, univariate analysis showed increased spinal BMAT-FF in the two most active walking groups (Table 4). This result, however, did neither show a consistent behavior in regard to β-values with lower β-values in the most active walking group compared to the second most active group; nor was there consistent behavior throughout the four models in multivariable analysis despite the fact that the most active walking group was the largest group in our study (42% of subjects) and therefore should provide the most statistical power. A dichotomous analysis of our walking parameter, dividing the most active (and largest) group (walking > 1 h/d; $n = 161$) from the lower walking groups (walking < 1 h/d; $n = 224$) did not show any significant differences in BMAT-FF (data not shown). Non-exercise cycling and job-related physical activity did not show any

Table 3 Unadjusted association of BMAT-FF with exercise. β-coefficient is expressing change in percentage points BMAT-FF

Exercise	BMAT-FF, L1		BMAT-FF, L2		BMAT-FF, RH		BMAT-FF, LH	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
≥ 2 h per week, regularly	− 3.94 (− 6.7; − 1.19)	0.005	− 3.51 (− 6.33; − 0.69)	0.02	− 1.02 (− 3.18; 1.14)	0.35	− 0.71 (− 2.85; 1.42)	0.51
~ 1 h per week, regularly	− 2.42 (− 5.13; 0.28)	0.08	− 1.96 (− 4.72; 0.81)	0.17	− 0.24 (− 2.42; 1.94)	0.83	− 0.38 (− 2.51; 1.75)	0.72
~ 1 h per week, irregularly	− 2.18 (− 5.50; 1.14)	0.20	− 2.8 (− 6.21; 0.61)	0.11	− 1.62 (− 4.3; 1.07)	0.24	− 1.63 (− 4.29; 1.03)	0.23
No exercise	Ref		Ref		Ref		Ref	

BMAT-FF bone marrow adipose tissue fat fraction

L1: vertebral body L1. L2: vertebral body L2. RH: right hip. LH: left hip. Ref: reference group used in the respective analysis

Table 4 Multivariable association of spinal BMAT-FF with exercise, non-exercise walking, non-exercise cycling, and job-related physical activity. Spinal BMAT-FF is averaged L1 and L2 BMAT-FF measurements. β-coefficient is expressing change in percentage points BMAT-FF. Model 1 included age and gender; model 2 included age, gender, and WC; model 3 included age, gender, WC, and glucose tolerance (normal glucose tolerance/prediabetes/diabetes mellitus); model 4 included age, gender, WC, glucose tolerance, and exercise as potential confounders

	Univariate		Model 1		Model 2		Model 3		Model 4	
Spine	BMAT-FF		BMAT-FF		BMAT-FF		BMAT-FF		BMAT-FF	
	β	p	β	p	β	p	β	p	β	p
Workout										
≥ 2 h per week, regularly	− 3.75 (− 6.51; − 0.99)	0.008	− 3.87 (− 6.26; − 1.48)	0.002	− 3.49 (− 6; − 0.99)	0.006	− 3.44 (− 5.97; − 0.9)	0.008	N/A	N/A
~ 1 h per week, regularly	− 2.2 (− 4.9; 0.5)	0.11	− 0.83 (− 3.21; 1.54)	0.49	− 0.6 (− 3.02; 1.82)	0.63	− 0.56 (− 3; 1.88)	0.65	N/A	N/A
~ 1 h per week, unregularly	− 2.56 (− 5.89; 0.78)	0.13	− 1.33 (− 4.23; 1.57)	0.37	− 1.19 (− 4.1; 1.73)	0.42	− 1.21 (− 4.15; 1.72)	0.42	N/A	N/A
No or nearly no activities	Ref		Ref		Ref		Ref		Ref	
Job-related physical activity										
Heavy physical labor	− 0.1 (− 5.84; 5.64)	0.97	1.25 (− 3.78; 6.28)	0.63	1.05 (− 3.97; 6.07)	0.68	1.08 (− 3.97; 6.13)	0.67	0.65 (− 4.39; 5.7)	0.80
Moderate physical labor	0.86 (− 1.72; 3.44)	0.51	0.49 (− 1.81; 2.8)	0.68	0.22 (− 2.09; 2.54)	0.85	0.2 (− 2.13; 2.53)	0.87	0.26 (− 2.07; 2.58)	0.83
Light physical labor	2.57 (0.13; 5.01)	0.04	0.3 (− 1.92; 2.51)	0.79	0.2 (− 2.01; 2.41)	0.86	0.2 (− 2.03; 2.43)	0.86	0.48 (− 1.74; 2.7)	0.67
No physical labor	Ref		Ref		Ref		Ref		Ref	
Non-exercise walking										
> 1 h	5.19 (1.09; 9.28)	0.01	2.57 (−1.06; 6.19)	0.16	2.44 (−1.17; 6.06)	0.19	2.43 (−1.19; 6.06)	0.19	3.1 (−0.53; 6.72)	0.09
0.5–1 h	5.34 (1.15; 9.53)	0.01	4.08 (0.4; 7.76)	0.03	3.92 (0.25; 7.6)	0.04	3.95 (0.26; 7.63)	0.04	4.5 (0.82; 8.19)	0.02
0.25–0.5 h	1.94 (− 2.5; 6.38)	0.39	1.79 (− 2.11; 5.68)	0.37	1.75 (− 2.13; 5.63)	0.38	1.75 (− 2.15; 5.64)	0.38	2.08 (− 1.79; 5.95)	0.29
< 0.25 h	Ref		Ref		Ref		Ref		Ref	
Non-exercise cycling										
> 1 h	1.94 (− 1.29; 5.17)	0.24	− 0.15 (− 2.99; 2.7)	0.92	0.02 (− 2.83; 2.86)	0.99	0.04 (− 2.82; 2.89)	0.98	1.39 (− 1.57; 4.34)	0.357
0.5–1 h	2.41 (− 0.38; 5.19)	0.09	0.98 (− 1.46; 3.43)	0.43	1.01 (− 1.43; 3.45)	0.42	0.98 (− 1.47; 3.43)	0.43	1.65 (− 0.84; 4.13)	0.193
0.25–0.5 h	0.75 (− 2.34; 3.85)	0.63	0.3 (− 2.42; 3.01)	0.83	0.43 (− 2.27; 3.14)	0.75	0.43 (− 2.28; 3.14)	0.76	0.73 (− 2.01; 3.48)	0.599
< 0.25 h	Ref		Ref		Ref		Ref		Ref	

BMAT-FF bone marrow adipose tissue fat fraction, *N/A* not applicable

L1: vertebral body L1. L2: vertebral body L2. RH: right hip. LH: left hip. Ref: reference group used in the respective analysis

Table 5 Multivariable association of hip BMAT-FF with exercise, non-exercise walking, non-exercise cycling, and job-related physical activity. Hip BMAT-FF is averaged RH and LH-BMAT-FF. β-coefficient is expressing change in percentage points BMAT-FF. Model 1 included age and gender; model 2 included age, gender, and WC; model 3 included age, gender, WC, and glucose tolerance (normal glucose tolerance/prediabetes/diabetes mellitus); model 4 included age, gender, WC, glucose tolerance, and exercise as potential confounders

	Univariate		Model 1		Model 2		Model 3		Model 4	
Hip	BMAT-FF		BMAT-FF		BMAT-FF		BMAT-FF		BMAT-FF	
	β	p	β	p	β	p	β	p	β	p
Workout										
≥ 2 h per week, regularly	− 1.02 (− 3.24; 1.2)	0.36	− 0.79 (− 2.82; 1.25)	0.45	− 1.99 (− 3.99; 0)	0.05	− 1.9 (− 3.9; 0.1)	0.06	N/A	N/A
~ 1 h per week, regularly	− 0.46 (− 2.69; 1.77)	0.69	0.61 (− 1.47; 2.68)	0.56	− 0.24 (− 2.24; 1.76)	0.812	− 0.25 (− 2.25; 1.75)	0.80	N/A	N/A
~ 1 h per week, unregularly	− 1.7 (− 4.48; 1.08)	0.23	− 1.22 (− 3.77; 1.33)	0.35	− 1.95 (− 4.39; 0.49)	0.117	− 2.09 (− 4.56; 0.38)	0.10	N/A	N/A
No or nearly no activities	Ref		Ref		Ref		Ref		Ref	
Job-related physical activity										
Heavy physical labor	0.6 (− 3.57; 4.77)	0.78	0.56 (− 3.27; 4.4)	0.77	1.1 (− 2.58; 4.78)	0.557	0.99 (− 2.7; 4.68)	0.60	0.66 (− 3.05; 4.38)	0.72
Moderate physical labor	− 0.88 (− 2.98; 1.22)	0.41	− 0.92 (− 2.89; 1.05)	0.36	− 0.4 (− 2.31; 1.5)	0.678	− 0.71 (− 2.65; 1.23)	0.47	− 0.45 (− 2.41; 1.5)	0.65
Light physical labor	0.4 (− 1.6; 2.41)	0.69	0.26 (− 1.64; 2.16)	0.79	0.4 (− 1.43; 2.22)	0.67	0.08 (− 1.78; 1.94)	0.93	0.19 (− 1.67; 2.06)	0.84
No physical labor	Ref		Ref		Ref		Ref		Ref	
Non-exercise walking										
> 1 h	− 0.55 (− 3.71; 2.62)	0.73	− 1.69 (− 4.66; 1.27)	0.26	− 1.59 (− 4.42; 1.25)	0.27	− 1.63 (− 4.46; 1.21)	0.26	− 1.57 (− 4.4; 1.27)	0.28
0.5–1 h	− 0.19 (− 3.47; 3.1)	0.91	− 0.44 (− 3.48; 2.61)	0.78	− 0.33 (− 3.24; 2.59)	0.824	− 0.33 (− 3.25; 2.59)	0.82	− 0.32 (− 3.23; 2.6)	0.83
0.25–0.5 h	− 2.14 (− 5.64; 1.36)	0.23	− 2.24 (− 5.45; 0.98)	0.17	− 2.05 (− 5.13; 1.02)	0.189	− 1.91 (− 4.99; 1.17)	0.22	− 1.97 (− 5.03; 1.08)	0.20
< 0.25 h	Ref		Ref		Ref		Ref		Ref	
Non-exercise cycling										
> 1 h	− 0.2 (− 2.67; 2.27)	0.87	− 1.27 (− 3.59; 1.05)	0.28	− 1.39 (− 3.61; 0.82)	0.217	− 1.36 (− 3.58; 0.86)	0.23	− 0.61 (− 2.96; 1.74)	0.61
0.5–1 h	1.15 (− 1.11; 3.41)	0.32	0.4 (− 1.72; 2.53)	0.71	0.32 (− 1.72; 2.35)	0.758	0.24 (− 1.79; 2.27)	0.82	0.66 (− 1.41; 2.73)	0.53
0.25–0.5 h	1.83 (− 0.6; 4.26)	0.14	0.42 (− 1.88; 2.71)	0.72	0.17 (− 2.02; 2.37)	0.877	0.18 (− 2.01; 2.38)	0.87	0.27 (− 1.96; 2.5)	0.81
< 0.25 h	Ref		Ref		Ref		Ref		Ref	

BMAT-FF bone marrow adipose tissue fat fraction, *N/A* not applicable

L1: vertebral body L1. L2: vertebral body L2. RH: right hip. LH: left hip. Ref: reference group used in the respective analysis

significant association with BMAT-FF in either location at any level of activity (Tables 4 and 5).

Discussion

Our study investigated the association of different levels of physical activity with BMAT-FF at two commonly investigated anatomical locations in a broad adult population. We found, that a significant association between exercise and lower levels of BMAT-FF was apparent in the spine but not in the proximal femur (Fig. 3). Non-exercise levels of physical activity, as in our walking, cycling, and job-related physical activity groups, were not sufficient to produce a consistently lower BMAT-FF in regard to the respective reference groups in neither the spine nor the proximal femur. Overall, we found a minimum of 2 h of exercise per week was required to display significantly lower BMAT-FF.

Compared to previous research in humans which preferably looked at young athletic, even amenorrhoeic populations [37, 39, 45], our cohort showed an average BMI of 28.1 kg/m^2, roughly in the range of western population, e.g., in Germany of 25.9 kg/m^2 (2013; [46]) or the USA of 28.8 kg/m^2 (male) and 29.5 kg/m^2 (female) (2013–2014; [47]). Our most active exercise group had an average BMI of 26.7 kg/m^2 and a WC of 94.3 cm, therefore still considered preobese (WHO definitions; [48]) and generally prompting a recommendation for weight loss [49].

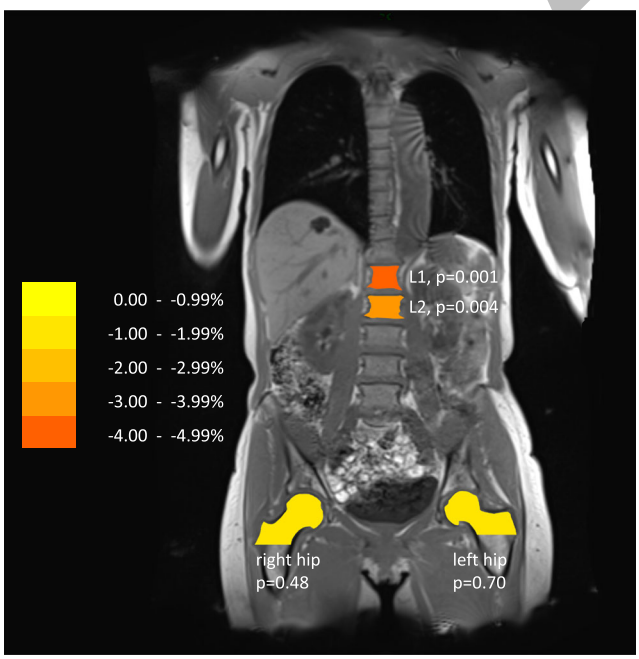

Fig. 3 Bland-Altman plots for inter-reader reproducibility of BMAT-FF measurements vertebral body L1, vertebral body L2, left hip, (LH) or right hip (RH)

The most similar study, to our knowledge, is probably the recent study by Belavy et al [37], not least because they also employed a 2-point Dixon MRI sequence similar to our approach. In contrast to our study, they looked at spinal BMAT in a young athletic population. Their long-distance running group required "running of at least 50 km per week for at least 5 years" [37]. Their control group "included subjects who have performed no regular sport or exercise in the last 5 years, currently engaging in less than 150 min of moderate activity per week and walked less than 15 min to or from their place of work" [37]. The different focus of investigation between Belavy's and our study is evident by the age distribution (25–35 years vs. mean 56 years, respectively) and the BMI (24.6–21.9 kg/m^2 in control to long-distance runners vs. 30.0–26.7 kg/m^2 in reference group to most active exercise group, respectively). Despite those differences, we similarly found that physical activity is significantly correlated with lower levels of spinal BMAT-FF, albeit to a different extend. Our most active exercise group exhibited 3.9 and 3.5 percentage points lower BMAT-FF in L1 and L2, respectively, lower than what Belavy et al found in their long-distance runners with 5.6 percentage point compared to their respective control group [37].

While it is inherently difficult to compare study groups across different studies with different control groups, it is nonetheless interesting to look at our highest exercise group in contrast to Belavy's athletic high-volume cycling group. Their high-volume cycling group required bicycle "riding at least 150 km per week, with at least three 50-km sessions per week, for at least the last 5 years and perform no other sport or exercise type more than once per week" [37]. Our most active exercise group, in absolute terms still an overweight group, did show significantly lower BMAT-FF which was not found in Belavy's athletic high-volume cycling group. This discrepancy could be explained by a mechanism that has been proposed to regulate BMAT. Several in vitro and animal in vivo experiments have found that mechanical stress, or inversely, mechanical unloading on bone, stimulates bone marrow change. It has been shown that mechanical stimuli inhibit adipocyte differentiation and favor osteoblastogenesis in bones with the differentiation of bone marrow stromal cells into either adipocytes or osteoblasts [29, 30, 32, 34]. Most exercises like running exert repetitive mechanical loading on the spine that is missing with cycling. Belavy et al consequently attributed the differences in BMAT-FF between their high-volume running and high-volume cycling groups to this mechanism. This mechanism was also supported by Rantalainen et al who looked at female athletes separated into impact and nonimpact loading sports, which included swimming [39]. This mechanism would also explain why our more unathletic, but likely mixed-exercise group could show lower BMAT-FF while a highly athletic, but purely cycling group did not. This suggests that this mechanism might be quite

pronounced in humans and very different from other fat depots like abdominal, visceral, or subcutaneous fat that are governed by energy consuming exercises including cycling and swimming [20, 22, 50]. Proximal femoral BMAT-FF, however, did not show this behavior in our study.

While BMAT as a whole differs from other human fat compartments [1, 13, 45], it seems in itself heterogeneous in a way not yet fully understood. The results of physical activity on human spinal BMAT showed consistent behavior in Belavy's [37] and our paper, also consistent with in vitro and in vivo animal models, as mentioned above. Rantalainen et al delineated concordant results for human mid-tibial BMAT on human subjects divided into impact and nonimpact loading sports [39]. As it has been recently suggested as a next step in BMAT research [37], we looked at the spine and lower extremity in the same subject. We specifically looked at a lower extremity site much more similar in bone composition to the spine, with greater amounts of red marrow and cancellous bone, compared to diaphyseal marrow that Rantalainen et al looked at [39] which in adults almost exclusively contains yellow marrow [51]. Our data showed that BMAT-FF in the spine and proximal femur are poorly correlated with each other (Fig. 2), and that BMAT-FF was not significantly associated with physical activity in the proximal femur (Table 4, Appendix E3). While raw measurements in the proximal femurs showed lower BMAT-FF in all three exercise groups compared to control in both locations (right and left), this happened to a much lower extend (around 1 percentage point; Table 4, Appendix E3), and since it did not reach significance, the validity of this observation remains speculative. This is also in contrast to animal models were lower extremities consistently showed a significant inverse relationship of BMAT with physical activity.

Possible explanations include that physical activity only affects diaphyseal BMAT in humans, or that rodent BMAT physiology is different from humans. Some rodent experiments could lack comparability due to different subsites of examination, e.g., when femurs were cut below the femoral head [30, 31] or when tibial BMAT was assessed [29, 34]. Also, a larger number of hip measurements or higher levels of physical activity could have demonstrated a significant association with hip BMAT-FF in our cohort.

The following considerations would support the latter concept. While it is difficult to compare results across different studies, our study looked at a more continuous spectrum of physical activity in an average, in absolute terms a likely quite unathletic population. Rantalainen et al on the other hand looked at athletes versus non-athletes [39]. This likely larger difference in physical activity between groups might have been the determining factor in eliciting a significant disparity in BMAT in the lower extremity between control and exercise groups. A similar constellation could be in play in animal models between caged controls with restricted movement versus exercise groups with, e.g., about 12 km of voluntary running per day on a running wheel [30].

The relationship of BMAT with BMD shows an inverse correlation in general [52, 53] and with physical activity [39]. However, more research accumulates that this inverse relationship holds not always true [13, 54]. How this behaves for different forms of physical activity at different body sites is something to be explored in the future.

Limitations

Our observational, non-experimental study design cannot establish a causative relationship between physical activity and BMAT-FF. Also, physical activity assessment could be hampered by recall bias. A possible confounder was its design as a case-control study focused on prediabetes and diabetes. 25% of subjects had prediabetes, 14% had diabetes. This, however, roughly represents numbers of the general population. In Germany, 9.8% of the population have diabetes (diagnosed) [55], 12% of the US population have diabetes (diagnosed and undiagnosed) [56], 16% of the population (age 55–74) show impaired glucose tolerance in Germany [57], and 34% show prediabetes in the USA [56]. Additionally, we adjusted for prediabetes and diabetes in our multivariable models to account for possible confounding effects, where no relevant confounding was observed. Also, our MRI sequence did not account for T2* effects, therefore, e.g., likely underestimating short T2* water species bound to or affected by the mineral bone matrix, macromolecules, or iron, and therefore likely overestimating fat fraction compared to other methods like MR spectroscopy [58]. However, this analysis looked at relative differences between groups and was not focused on estimating absolute values as closely as possible.

Conclusion

Physical activity is inversely associated with spinal BMAT-FF, but not proximal femoral BMAT-FF, in a population-based cohort study when exercising for more than 2 h per week. Our data, in context with previous research, supports the idea that BMAT is regulated through mechanical impact stress on bones. This effect seems to happen at least preferentially in the spine as opposed to the proximal femur.

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Compliance with ethical standards

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Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in several studies, however not in relation to bone marrow adipose tissue, so there is no overlap.

Methodology
- retrospective
- cross-sectional study
- performed at one institution

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