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Publication Date

2020-03-01

DOI

10.1016/j.bone.2019.115198

Peer reviewed

Bone 132 (2020) 115198

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Objective measures of moderate to vigorous physical activity are associated with higher distal limb bone strength among elderly men

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ARTICLE INFO

Keywords:
Physical activity
Bone strength
Older men
Distal limbs
Compartmental BMD

ABSTRACT

Our aim was to determine the association between objectively measured physical activity (PA) and bone strength of the distal limbs among older men. We studied 994 men from the MrOS cohort study (mean age 83.9) who had repeat (Year 7 and 14) 5-day activity assessment with at least 90% wear time (SenseWearPro3 Armband) and Year 14 measures using high resolution peripheral quantitative tomography (HR-pQCT) (Scanco). Total energy expenditure (TEE), total steps per day, peak cadence (mean of top 30 steps/min over 24 h) and time spent in a given level of activity: sedentary (reference, < 1.5 metabolic equivalents of task [METs]), light (1.5 to < 3 METs), or moderate to vigorous physical activity(MVPA: ≥3 METs) were calculated as mean over the two time points. Estimated failure load was determined from HR-pQCT data using finite element analysis. We used standardized variables and adjusted for potential confounders using linear regression. The means ± SDs for daily activity were: 2338 ± 356 kcal/d [TEE]; 5739 ± 2696 steps/day [step count], 60 ± 20 cpm [peak cadence], 67 ± 28 min/d [light activity], and 85 ± 52 min/d [MVPA]. Higher TEE, step count, and peak cadence were each associated with higher failure load of the distal radius (effect sizes respectively: 0.13 [95% CI: 0.05, 0.20], 0.11 [95% CI: 0.04, 0.18], and 0.08 [95% CI: 0.01, 0.15]) and higher failure load of the distal tibia (effect sizes respectively 0.21 [95% CI: 0.13, 0.28], 0.19 [95% CI: 0.13, 0.26], 0.19 [95% CI, 0.13, 0.25]). Time spent in MVPA vs. time sedentary was related to bone strength at both sites after adjustment, whereas time spent in light activity vs. time sedentary was not. TEE was associated with compartmental area and BMD parameters at distal tibia, but only area parameters at the distal radius. In summary, MVPA over a 7-year period of time may have a modest association with bone strength and geometry among older men.

1. Introduction

It is well known that physical activity (PA) has a role in the development and maintenance of bone over the lifespan. Studies in young men have shown that the association between PA and bone strength depends on type of PA, including magnitude and frequency of applied force [1–3]. Similarly, high loading as a result of occupation was also associated with higher bone strength in working age men [4]. Whereas these studies suggest an association between activity and bone strength, the association between activity and bone strength is less clear among

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https://doi.org/10.1016/j.bone.2019.115198
Received 30 September 2019; Received in revised form 17 December 2019; Accepted 18 December 2019
Available online 20 December 2019

men in the 8th and 9th decades of life. There is a marked decline in both overall activity and moderate to vigorous physical activity (MVPA) with increasing age [5]. Longitudinal analysis has shown that the trajectories of bone microarchitecture, on average, in oldest age cohorts are different from those of younger adults [6].

A few studies have examined PA and bone microstructure and strength in adults late in life. One study among older Swedish men found that self-reported PA during growth and young adulthood was associated with high-resolution peripheral quantitative computed tomography (HR-pQCT) parameters at the distal tibia, including cross-sectional area and cortical thickness late in life, but that current self-reported PA was not associated with failure load calculated using finite element analysis at either the radius or tibia [7]. Another cross-sectional study in older Swedish women found that self-reported PA was related to cortical thickness and cross-sectional area at the ultra-distal tibia, but again PA was not related to failure load [8]. Thus, it is unclear if the null findings from these studies reflect the absence of an association between PA and bone microstructure and strength late in life, or if inaccurate assessment of PA by self-report (time, intensity, habitual levels) [9] resulted in bias towards the null. Activity monitors can provide more accurate global measures of PA (e.g. total energy expenditure or step count), measures of peak activity, as well as more detailed time distribution of the intensity of PA.

Therefore, our primary objective was to determine the independent association of objectively measured PA including mean daily total energy expenditure (TEE), total step count, peak cadence, and time spent at given PA activity levels (sedentary, light, moderate to vigorous) over a period of 7 years with bone strength and microarchitecture of the distal radius and tibia in older community-dwelling men.

2. Methods

2.1. Study population

From 2000 to 2002, 5994 ambulatory men ≥65 years old were recruited from six geographic areas of the United States and enrolled in the Osteoporotic Fractures in Men (MrOS) Study, a prospective cohort study [10,11]. Between May 2014 and May 2016 all active MrOS participants were invited to participate in the Year 14 visit and 1801 attended the Year 14 Visit and had an HR-pQCT scan (Fig. 1). Men were eligible for the present study if they had Year 7 and Year 14 activity monitor data for five 24-hour periods with at least 90% wear time and non-missing covariates and had HR-pQCT data at the Year 14 visit (N = 994). The analytic sample for distal radius (N = 948) and distal tibia (N = 951) was smaller due to missing scan site, motion artifact, or anatomic findings. Signed informed consent was obtained from all study participants in accordance with the Helsinki Declaration. Detailed study information may be found at the MrOS Online website (http://mrosdata.sfcc-cpmc.net).

2.2. Objective physical activity

At the Year 14 exam, men were provided the SenseWear® Pro3 Armband (Body Media, Inc., Pittsburgh, PA) and instructed to wear it on their right arm continuously for the next week with the exception of brief periods (e.g. bathing). The monitor uses six sensors (2-axis accelerometer, a heat flow sensor, galvanic skin response, skin temperature sensors, and ambient temperature sensors) to collect physiological data in 1-minute epochs. Data collection began at midnight on the first day and accrued by each complete 24-hour period thereafter. Monitor data was combined along with height, weight, handedness, and smoking as inputs in proprietary algorithms (Innerview Professional 5.1 software, Body Media, Inc.; Pittsburgh, PA) to estimate total step counts per day and TEE in kilocalories per day (kcal/d). Peak cadence was obtained from data by ordering cadence (counts/minute) by 1-minute episodes and then taking mean of the top 30 episodes [12].

Two validation studies comparing the SenseWear® Pro Armband with the criterion method of doubly labeled water showed acceptable levels of agreement for TEE [13,14]. Standard cut-points based on metabolic equivalents of task (METs) were used to categorize level of PA: sedentary activity (< 1.5 METs), light activity (1.5 to < 3 METs), MVPA (≥3 METs) [15]. The activity monitor was also used to classify sedentary time into sleep vs. non-sleep sedentary time. Studies comparing armband with indirect calorimetry showed bias and misclassification of vigorous activity, but showed better classification of light and moderate activity [16,17]. In the present study moderate (≥3 to < 6 METs) and vigorous activity (≥6 METs) were combined due to infrequency of vigorous activity, i.e. median (interquartile range) 5 [2–11] minutes.

2.3. Measurement of bone strength and architecture

HR-pQCT measures were performed as previously described [18]. Briefly, centrally-trained operators performed scans of the radius from the non-dominant arm (9 mm from the articular surface) and the tibia from the ipsilateral leg (22 mm from the articular surface) using Scanco XtremeCT II machines (Scanco Medical AG, Brüttisellen, Switzerland) [19]. Exceptions were made in the case of prior fracture, metal shrapnel or implant, or recent non-weight bearing loads > 6 weeks; 8% of radius scans and 8% of tibia scans were performed on the dominant limb. Each center had local phantom scanned on a daily basis to monitor for values that fall outside of the nominal range (8 mg HA/cm^3). A single phantom was circulated between the clinical centers and the resulting between-site calibration coefficients were all < 0.6%; therefore, pooled data was used without transformations [20].

Motion artifacts were graded using an established semi-quantitative 5-point grading system and low quality images were excluded [21]. Segmentation failures were flagged by measuring slice-wise variation in total cross-sectional area using fully automated pipeline; scans with absolute slice-wise difference of 4 mm^2 (< 6% of scans) were visually reviewed and manually corrected [22]. Statistical outliers were flagged for review; those with abnormal anatomic findings (e.g. severe inflammatory arthritis, osteolytic lesions, injuries with ossification, unreported fracture) were then excluded.

Limb length (ulna and tibia) was measured at time of the scan. Volumetric BMD (vBMD) and cross-sectional area of the total, cortical, and trabecular compartments were measured. Cortical porosity and thickness, and trabecular thickness and number were calculated directly. Linear elastic micro-finite element analysis of a 1% uniaxial compression was performed using a homogenous elastic modulus of 10 GPa and a Poisson's ratio of 0.3 (Scanco FE Software v1.12, Scanco Medical). The failure load was estimated by calculation of the reaction force at which 7.5% of the elements exceed a local effective strain of 0.7% [23].

2.4. Other measurements

Demographics were obtained from standardized questionnaires at baseline including self-race/ethnicity (non-Hispanic white vs. other) and education (length/degree). Lifestyle and anthropometric variables were obtained at the Year 14 clinic visit. Smoking history was categorized in two categories (ever vs. never with cutoff of at least 100 total cigarettes). Alcohol use was categorized by self-reported intake (low: < 1 drink/wk., moderate: 1–13 drinks/wk., high: 14+ drinks/wk). Body weight (kg) and height (m) were measured and body mass index was calculated in kg/m^2. Chronic conditions were self-reported and included myocardial infarction, stroke, congestive heart failure, diabetes, cancer, COPD, rheumatoid arthritis, osteoarthritis, depression, visual impairment, Parkinson's disease, and Alzheimer's disease. A comorbidity index was created summing the total number of self-reported medical conditions together with fall history and history of hip fracture [24]. Self-reported PA at all clinic visits was assessed using the

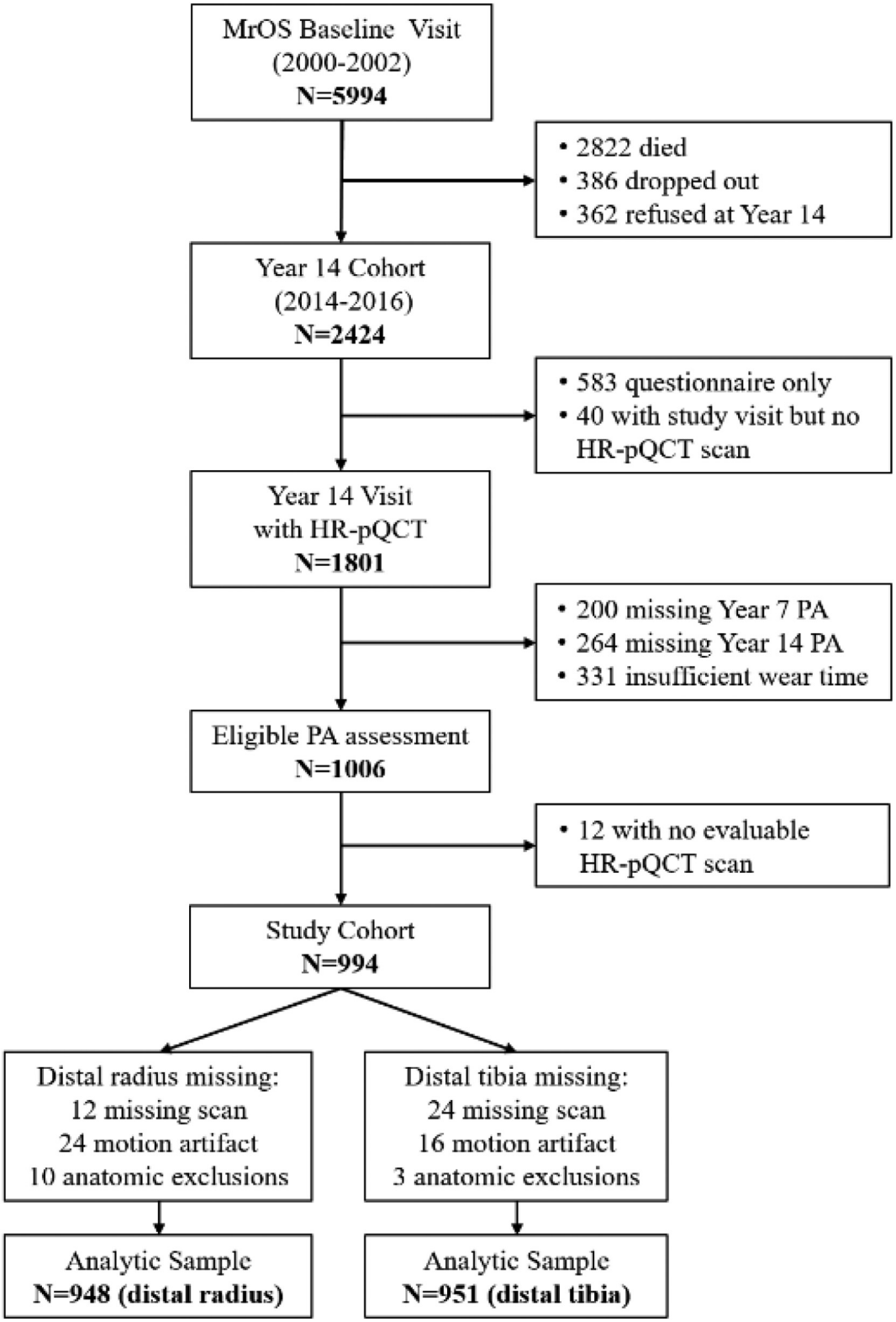

Fig. 1. Study flow diagram.

Physical Activity Scale for the Elderly (PASE) [25].

2.5. Statistical analysis

We used chi-squared and *t*-tests to compare men included vs excluded from the analytical cohort and chi-square tests and ANOVA for comparisons of participant characteristics by quartile of TEE. The threshold for all statistical tests was $p = 0.05$. We used multiple linear regression models to determine the association between PA measures expressed as continuous variables and HR-pQCT parameters. TEE was the primary exposure and failure load was the primary outcome. For each participant, the primary measures of each PA variable was defined to be the mean value of the Year 7 and Year 14 measures to reflect the trajectory level of PA during this 7-year period in this cohort. We have

previously analyzed the trajectories of PA over time in the MrOS cohort based on the PASE score and shown that while PA declines over time, trajectories of PA were roughly parallel [26]. Thus, we expected that the rank order of the objective PA also remained fairly stable; thus a mean PA of the 2 time points would reflect the primary parameter of these declining trajectories during the 7-year period. To standardize effect sizes, all outcome HR-pQCT measures and the continuous main predictor variables (TEE, step count, peak cadence) were then transformed to have mean = 0 and SD = 1.

We used an isotemporal substitution model for time variables since these variables necessarily sum to 24 h [27]. Daily time was divided into three categories by level of activity. The reference category was sedentary time, which included sleep time, nap time, and time quietly sitting. The comparison categories were time spent in light PA and time spent in MVPA, each with unit measure of 30-minute increments for ease of use in knowledge translation. Models included both light activity time and MVPA time variables but did not include the reference category due to collinearity. The parameters for time in light activity reflect an exchange between light activity time and sleep/sedentary time due to the adjustment for time in MVPA.

We considered base models including only variable of interest and adjusted models which include variable of interest as well as a priori specified confounders including age, race, education, clinical center, smoking, alcohol use, limb length, weight, and comorbidity index. We assessed all continuous variables for possible non-linearity using higher order terms and fractional polynomials. To further clarify relationships between change in PA over time and estimated failure load, we performed *post-hoc* analyses with each time point of objective physical activity separately as a predictor and a joint analysis with both time points included as predictors. We also performed *post-hoc* analyses to assess whether associations were independent of self-reported PA and whether there was any difference in outcome parameters when treating sleep and sedentary time as separate categories. Analysis was performed using Stata Version 15.0 (College Station, TX).

3. Results

Among the 994 men in the analytic cohort (Fig. 1), mean ± SD age was 83.9 ± 3.9 years, with range 77–98 years. Supplemental Tables 1 and 2 show a comparison of baseline characteristics of those included vs. excluded from the analytical cohort. Men in the study sample were slightly younger, had fewer chronic conditions, had slightly greater alcohol consumption, and were more likely to be college educated than those excluded for missing exposure or outcome variable. Despite demographic differences, men included in the study sample had very similar bone microarchitecture parameters to those who were excluded due to missing PA. Table 1 shows the characteristics of the cohort overall and stratified by quartile of TEE. Men with higher TEE were younger and had fewer chronic conditions; were more likely to be non-Hispanic white; and had higher height, weight, and BMI. All measures of PA, including historical self-reported measures, were higher in quartiles with higher TEE. Mean step count increased across quartiles of TEE with at least 1000 steps/day difference between adjacent quartiles. Table 2 shows HR-pQCT measures of the cohort overall and stratified by quartile of TEE. Men with higher TEE had longer limbs, greater trabecular # and cross-sectional areas, and higher estimated failure load of both the distal radius and tibia. Men with higher TEE also had slightly higher trabecular BMD at the distal tibia.

3.1. Distal radius

For the distal radius, higher TEE, step count, and peak cadence were each associated with higher failure load, with effect sizes ranging from 0.08 (95% CI: 0.02, 0.14) for peak cadence to 0.19 (95% CI: 0.13, 0.26) for TEE in unadjusted models (Table 3). Adjustment for confounders, including weight, resulted in a substantial attenuation of the association between TEE and failure load and the resulting effect size was 0.13 (95% CI: 0.05, 0.20). In contrast, adjusting for confounders had minimal impact on the strength of the association of step count or peak cadence with failure load. More time spent in MVPA vs. time sedentary was also modestly associated with higher distal radius failure load in unadjusted analysis (0.06 [95% CI: 0.01, 0.11] SD per 30 min) and adjusted analysis (0.08 [95% CI: 0.03, 0.13] SD per 30 min), whereas time spent in light activity vs. time sedentary was not associated with distal radius failure load in either analysis.

Fig. 2 shows the association between average TEE and HR-pQCT parameters of the distal radius including failure load as well as other more specific geometric and compartmental parameters. In addition to the previously noted association between TEE and failure load of the distal radius, higher average TEE was also associated with area parameters of the distal radius (i.e. higher total area, higher trabecular area, and higher cortical area). Higher average TEE was not associated with total vBMD, compartmental vBMD, or any other compartmental parameter of the distal radius.

3.2. Distal tibia

For the distal tibia, higher TEE, step count, and peak cadence were also associated with higher failure load, with effect sizes ranging from 0.15 (95% CI: 0.09, 0.22) for peak cadence to 0.28 (95% CI: 0.22, 0.35) for TEE (Table 3). Adjustment for confounders including weight resulted in a substantial attenuation of the association between TEE and failure load with resulting effect size 0.21 (95% CI: 0.13, 0.28). In contrast adjusting for confounders resulted in slightly larger effect sizes for the association between step count and failure load and peak cadence and failure load. More time spent in MVPA vs. time sedentary was also associated with higher distal tibia failure load in unadjusted analysis (0.06 [95% CI: 0.01, 0.11] SD per 30 min) and adjusted analysis (0.10 [95% CI: 0.05, 0.15] SD per 30 min), whereas time spent in light activity vs. time sedentary was not associated with distal tibia failure load in either analysis.

Fig. 2 shows the association between average TEE and HR-pQCT parameters of the distal tibia. In addition to the previously noted association between TEE and failure load of the distal tibia, higher average TEE was also associated with area parameters of the distal tibia (i.e. higher total area, higher trabecular area, and higher cortical area). Higher average TEE was also associated with vBMD parameters of the distal tibia (i.e. higher total and cortical vBMD [$p < 0.05$] but not higher trabecular vBMD [$p = 0.06$]). Finally, higher average TEE was associated with higher cortical thickness, but was not associated with cortical porosity, trabecular number, or trabecular thickness.

3.3. Secondary analyses

In *post-hoc* analyses assessing Year 7 and Year 14 objective measures of TEE separately as predictors of failure load, we found that the association of TEE assessed at a single time point with failure load was similar to that in the primary analysis in which the mean of the two TEE at the two time points was used (Supplemental Table 3). In further analysis when TEE from the two time points were both included in the same model (i.e. mutually adjusted), we found that Year 7 TEE was a predictor of distal radius failure load, but Year 14 TEE was not (Supplemental Table 4). Thus, once initial level of physical activity was accounted for in the analysis, subsequent activity was no longer a predictor. In contrast, we found that both Year 7 TEE and Year 14 TEE were predictors of distal tibia failure load after accounting for each other with roughly equal weights. Analysis of other distal radius HR-pQCT measures using TEE from two time points (mutually adjusted) revealed that Year 7 TEE was also a predictor of total, trabecular, and cortical area parameters, whereas Year 14 TEE was not a predictor of any HR-pQCT parameter (Supplemental Fig. 1). Analysis of other distal tibia HR-pQCT measures using TEE from two time points (mutually

Table 1
Characteristics of study sample (N = 994) stratified by quartile of total energy expenditure.

Mean ± SD, N (%)	Cohort N = 994	Quartile 1 N = 249	Quartile 2 N = 248	Quartile 3 N = 249	Quartile 4 N = 248
Age, years	**83.9 ± 3.9**	**86.3 ± 4.1**	**83.9 ± 3.7**	**83.3 ± 3.6**	**82.2 ± 2.7**
# chronic conditions[a]	**2.0 ± 1.4**	**2.2 ± 1.4**	**2.1 ± 1.5**	**1.9 ± 1.5**	**1.9 ± 1.4**
Height (cm)	**172.5 ± 6.7**	**167.7 ± 5.3**	**171.8 ± 5.4**	**173.9 ± 6.3**	**176.5 ± 6.5**
Weight (kg)	**80.0 ± 12.5**	**72.6 ± 9.2**	**79.4 ± 10.5**	**81.0 ± 12.2**	**86.9 ± 13.3**
Body mass index (kg/m^2)	**26.9 ± 3.7**	**25.8 ± 3.0**	**26.9 ± 3.5**	**26.8 ± 3.9**	**27.9 ± 4.0**
Race/ethnicity (non-Hispanic white)	**898 (90.3)**	**210 (84.3)**	**229 (92.3)**	**231 (92.8)**	**228 (91.9)**
College education[b]	649 (65.3)	163 (65.5)	166 (66.9)	159 (63.9)	161 (64.9)
Ever Smoker (100+ lifetime cigarettes)	561 (56.4)	124 (49.8)	145 (58.5)	143 (57.4)	149 (60.1)
Alcohol (1+ drink/wk)[b]	517 (52.2)	120 (48.8)	133 (53.6)	130 (52.2)	134 (54.3)
TEE (kcal/d)	*2338 ± 356*	*1924 ± 133*	*2201 ± 62*	*2413 ± 68*	*2818 ± 232*
Steps	*5739 ± 2696*	*4088 ± 1915*	*5088 ± 2098*	*6331 ± 2525*	*7452 ± 2877*
Peak cadence (cpm)	*62.0 ± 20.3*	*52.4 ± 18.8*	*59.3 ± 19.1*	*66.8 ± 20.1*	*69.6 ± 18.8*
Light activity (min/d)	*66.9 ± 27.9*	*47.0 ± 19.0*	*61.0 ± 22.1*	*72.8 ± 22.9*	*86.9 ± 29.5*
MVPA (min/d)	*85.0 ± 52.1*	*46.3 ± 26.8*	*68.7 ± 30.1*	*92.9 ± 42.5*	*132.3 ± 58.3*

Abbreviations: TEE, total energy expenditure; MVPA, moderate to vigorous activity.
Quartile 1: 1520–2019.9 kcal/d, Quartile 2: 2092–2307.2 kcal/d, Quartile 3: 2307.3–2543.3 kcal/d, Quartile 4: 2543.8–3631.6 kcal/d.
Bold indicates p-value < 0.05; italics show other measures of activity correlated with TEE.
[a] Chronic conditions include fall history, hip fracture, myocardial infarction, stroke, congestive heart failure, diabetes, cancer, COPD, rheumatoid arthritis, osteoarthritis, depression, visual impairment, Parkinson's disease, and Alzheimer's disease.
[b] Education and alcohol use collapsed to two categories for simplicity.

adjusted) revealed that Year 7 TEE was also a predictor of total, trabecular, and cortical area parameters, while Year 14 TEE was a predictor only of failure load and cortical vBMD (Supplemental Fig. 2). In other *post-hoc* analyses, there was a very slight attenuation in the associations of objective measures of PA with estimated failure load at the radius or tibia after further adjustment for self-reported PA and no overall difference between sleep vs sedentary activity excluding sleep with respect to any HR-pQCT outcome (data not shown).

4. Discussion

We found that higher levels of objectively measured PA, as determined by TEE, step count, and peak cadence, were all associated with higher failure load of the distal radius and the distal tibia among community-dwelling older men. The associations were slightly stronger at the distal tibia, a weight-bearing site vs. the distal radius, a non-weight bearing site. Our study used repeat measure of objective activity as an exposure variable, thus reflecting the cumulative activity over the previous 7-year period. These associations were very similar whether we used prior PA measures from the Year 7 visit, current measures from the Year 14 visit, or the mean measures from these two visits. However, when mutually adjusted, PA at both time points had a similar association with the failure load of the distal tibia, but only the initial time point of PA was associated with failure load at the distal radius. We also found that greater time spent in MVPA (vs. time sedentary) was associated with higher bone strength at both the distal radius and distal tibia, whereas time spent in light activity and time spent sleeping (vs. time sedentary) were not. This pattern of associations is consistent with biological mechanisms linking loading forces above a given threshold with bone remodeling.

Table 2
Bone strength, microarchitecture, and geometry stratified by quartile of total energy expenditure.

	Mean ± SD, N (%)	Cohort	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Distal radius	**Limb length (mm)**	**286 ± 14**	**280 ± 13**	**285 ± 13**	**288 ± 13**	**293 ± 15**
N = 948	**Failure load (kN)**	**4.9 ± 1.3**	**4.5 ± 1.2**	**4.8 ± 1.2**	**5.1 ± 1.4**	**5.2 ± 1.4**
	BMD (mg/cm^3)	275 ± 61	273 ± 61	276 ± 59	278 ± 67	272 ± 58
	Area (mm^2)	**398 ± 66**	**370 ± 59**	**390 ± 59**	**405 ± 65**	**429 ± 68**
	Trabecular BMD (mg/cm^3)	170 ± 39	167 ± 40	170 ± 37	173 ± 41	172 ± 39
	Trabecular area (mm^2)	**337 ± 68**	**311 ± 61**	**329 ± 63**	**342 ± 68**	**365 ± 70**
	Trabecular thickness (mm)	0.25 ± 0.02	0.25 ± 0.02	0.25 ± 0.02	0.25 ± 0.02	0.25 ± 0.02
	Trabecular # (mm^{-1})	**1.41 ± 0.21**	**1.36 ± 0.21**	**1.41 ± 0.20**	**1.43 ± 0.22**	**1.42 ± 0.20**
	Cortical BMD (mg/cm^3)	798 ± 69	798 ± 69	801 ± 71	798 ± 70	796 ± 67
	Cortical area (mm^2)	**66 ± 14**	**63 ± 13**	**65 ± 14**	**68 ± 15**	**69 ± 13**
	Cortical thickness (mm)	0.96 ± 0.23	0.95 ± 0.22	0.96 ± 0.24	0.97 ± 0.24	0.95 ± 0.21
	Cortical porosity (%)	1.6 ± 0.8	1.7 ± 0.9	1.6 ± 0.8	1.5 ± 0.8	1.6 ± 0.8
Distal tibia	**Limb length (mm)**	**404 ± 25**	**393 ± 23**	**402 ± 23**	**407 ± 24**	**414 ± 24**
N = 951	**Failure load (kN)**	**13.6 ± 2.9**	**12.4 ± 2.4**	**13.4 ± 2.6**	**14.1 ± 3.1**	**14.6 ± 3.1**
	BMD (mg/cm^3)	281 ± 55	277 ± 54	280 ± 55	285 ± 58	283 ± 53
	Area (mm^2)	**894 ± 136**	**827 ± 120**	**884 ± 124**	**907 ± 128**	**957 ± 139**
	Trabecular BMD (mg/cm^3)	**186 ± 38**	**179 ± 37**	**184 ± 37**	**191 ± 39**	**188 ± 38**
	Trabecular area (mm^2)	**760 ± 146**	**701 ± 131**	**754 ± 138**	**772 ± 142**	**815 ± 149**
	Trabecular thickness (mm)	0.27 ± 0.02	0.27 ± 0.02	0.27 ± 0.02	0.27 ± 0.02	0.27 ± 0.02
	Trabecular # (mm^{-1})	**1.35 ± 0.21**	**1.30 ± 0.21**	**1.35 ± 0.21**	**1.37 ± 0.19**	**1.38 ± 0.21**
	Cortical BMD (mg/cm^3)	783 ± 81	776 ± 86	780 ± 91	782 ± 73	792 ± 73
	Cortical area (mm^2)	**139 ± 31**	**132 ± 29**	**136 ± 31**	**142 ± 33**	**147 ± 29**
	Cortical thickness (mm)	1.48 ± 0.34	1.46 ± 0.33	1.46 ± 0.34	1.49 ± 0.36	1.50 ± 0.32
	Cortical porosity (%)	4.3 ± 1.7	4.4 ± 1.8	4.2 ± 1.7	4.3 ± 1.7	4.1 ± 1.5

Quartile 1: 1520–2019.9 kcal/d, Quartile 2: 2092–2307.2 kcal/d, Quartile 3: 2307.3–2543.3 kcal/d, Quartile 4: 2543.8–3631.6 kcal/d.
Bold indicates p-value < 0.05.

Table 3
Associations[a] of objective measures of physical activity with estimated failure load of the distal radius and distal tibia.

		Distal radius failure load		Distal tibia failure load	
		Crude	Adjusted[b]	Crude	Adjusted[b]
TEE	Beta (95% CI)	**0.19 (0.13, 0.26)**	**0.13 (0.05, 0.20)**	**0.28 (0.22, 0.35)**	**0.21 (0.13, 0.28)**
	R-squared	3.8%	9.5%	8.0%	16.6%
Step count	Beta (95% CI)	**0.10 (0.04, 0.17)**	**0.11 (0.04, 0.18)**	**0.15 (0.09, 0.21)**	**0.19 (0.13, 0.26)**
	R-squared	1.0%	9.3%	2.3%	16.6%
Peak 30 min Cadence	Beta (95% CI)	**0.08 (0.02, 0.14)**	**0.08 (0.01, 0.15)**	**0.15 (0.09, 0.22)**	**0.19 (0.12, 0.25)**
	R-squared	0.6%	8.8%	2.4%	16.4%
Light activity	Beta (95% CI)	−0.04 (−0.14, 0.06)	−0.05 (−0.15, 0.05)	−0.04 (−0.13, 0.06)	−0.03 (−0.13, 0.07)
MVPA	Beta (95% CI)	**0.06 (0.01, 0.11)**	**0.08 (0.03, 0.13)**	**0.06 (0.01, 0.11)**	**0.10 (0.05, 0.15)**
	R-squared	0.7%	9.5%	0.8%	15.6%

Abbreviations: TEE, total energy expenditure; MVPA, moderate to vigorous activity. Bold indicated associations with p-value < 0.05.

[a] Beta coefficient is standardized effect size with corresponding SDs: TEE (SD = 356 kcal/d), steps (SD = 2696 steps/d), peak cadence (20.3 cpm). Beta coefficient is SD per 30 min/d increment (time variables). Light activity = activity with 1.5 to < 3 METs, moderate/vigorous activity = activity with ≥3 METs, reference category = sedentary time (< 1.5 METs).

[b] Models were adjusted for age, race, education, clinical center, smoking, alcohol use, limb length, weight, and # of chronic conditions (fall history, hip fracture, myocardial infarction, stroke, congestive heart failure, diabetes, cancer, COPD, rheumatoid arthritis, osteoarthritis, depression, visual impairment, Parkinson's disease, and Alzheimer's disease).

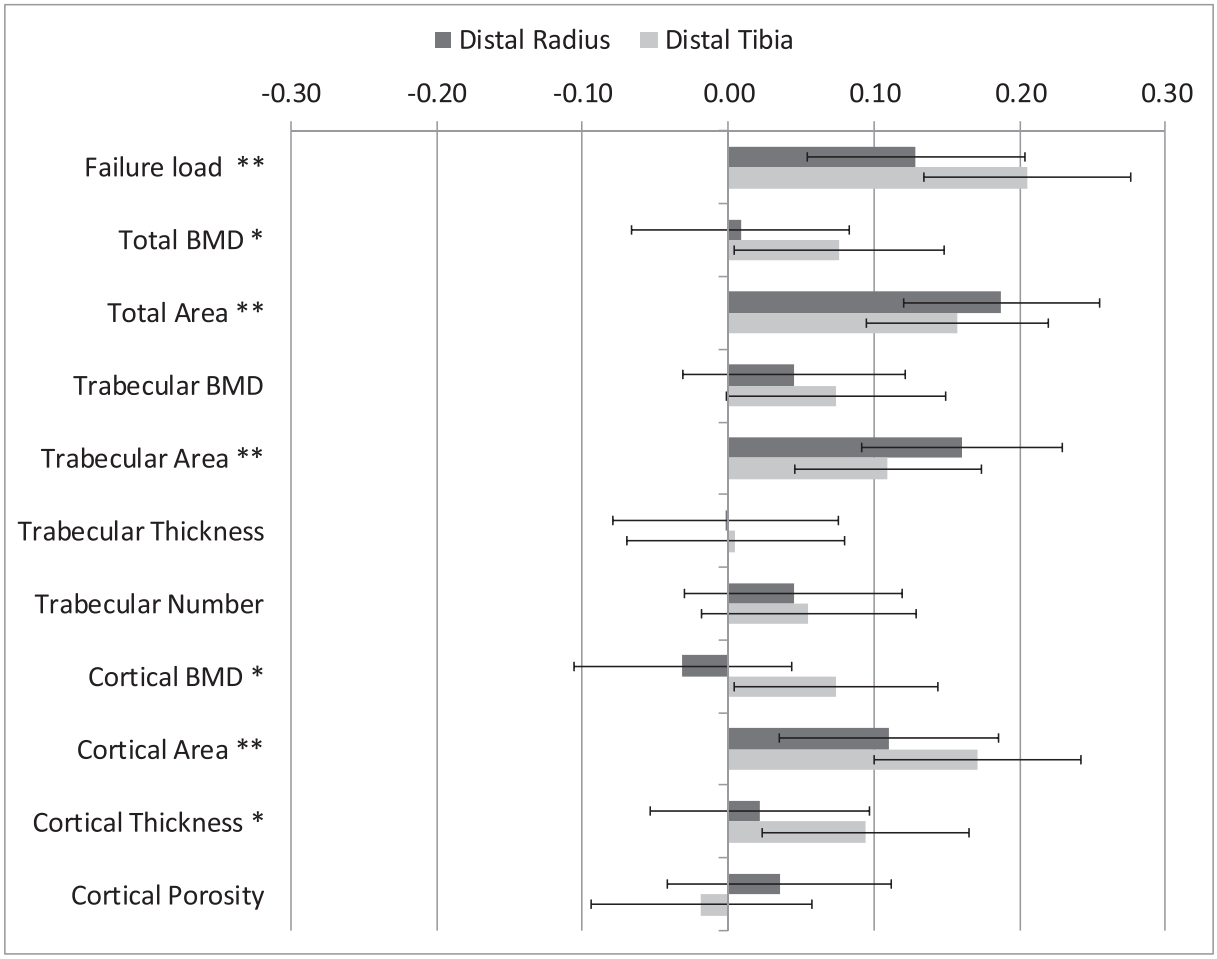

Fig. 2. The associations between total energy (TEE) expenditure and HR-pQCT parameters of the distal radius and distal tibia in fully adjusted models.
Bars indicate effect size for TEE (with SD = 356 kcal/d); whiskers indicate 95% confidence intervals. Statistically significant effect size indicated by * (tibia only) ** (both radius and tibia).
Models were adjusted for age, race, education, clinical center, smoking, alcohol use, limb length, weight, and # of chronic conditions (fall history, hip fracture, myocardial infarction, stroke, congestive heart failure, diabetes, cancer, COPD, rheumatoid arthritis, osteoarthritis, depression, visual impairment, Parkinson's disease, and Alzheimer's disease).

The association between TEE and distal radius failure load was attributable to bone size (total cross-sectional area) as there were no associations between TEE and compartmental vBMD or cortical thickness. Nilsson et al. found no association between current activity as assessed by PASE and any pQCT or HR-pQCT parameter of the radius based on a study of 597 Swedish men of roughly the same age [7]. The

discrepant findings between the current study and the Swedish study might be due to methods (objective activity vs self-report), increased sample size, repeated measures, or demographic differences. Longitudinal analysis has shown that the combination of endosteal resorption and periosteal expansion over time results in increased cross-sectional area of both the distal radius and tibia [28]. Thus, the association between higher PA and greater cross-sectional area in the present study suggests that there might be increased bone remodeling among those with higher PA levels.

The associations between activity and bone strength of the distal tibia are consistent with weight-bearing status and underlying biology linking loads to remodeling. The distal radius is non-load bearing, and thus any posited associations must relate to the smaller direct bone specific forces at the radius or other mechanisms. Direct causal effects are possible, notably since the activity monitor used in the study was an armband activity monitor. Counts detectable by the armband monitor could conceivably directly impact bone remodeling, although these effects would be smaller than those at a load bearing skeletal site. An alternate mechanism relates to the role of bone as a calcium reservoir. A longitudinal study by Vico et al. found that space flight had large and immediate effects on the distal tibia cortical thickness observable at the time of landing, but that effects on cortical thickness at the distal radius, while present, were smaller and not significant [29]. However, there were residual effects of space flight on bone after landing so that the cortical thickness of the distal radius continued to decrease after landing with a concurrent return to baseline for cortical thickness the distal tibia. In summary, the distal radius might be affected by loading and unloading of other skeletal sites over a longer time period. For the present study we note that both Year 7 and Year 14 PA were related to failure load at the distal tibia, while only the Year 7 PA was related to failure load at the distal radius.

The association between TEE and distal tibia failure load was attributable to bone size, cortical thickness, and compartmental vBMD. Here, our results were largely comparable to results from the Swedish study, with both studies showing larger associations for the weight bearing site [7]. In particular, Nilsson et al. found that current self-reported physical activity was associated with greater trabecular thickness, trabecular number, cortical thickness, and cortical vBMD at the distal tibia after both without and with adjustment for early adult activity. Our study found that objective activity measures were independent predictors of bone strength measures after adjusting for either current or previous self-reported activity. We were unable to assess whether early adulthood activity was related to bone strength or geometry as done in the Swedish study since measures of early adulthood activity are not available from the MrOS cohort. We did not find a statistically significant association between PA and trabecular BMD. However, we note that the point estimates are consistent with a possible positive association at the distal tibia and a larger study may be able to confirm this finding. Other possible reasons for the lack of an association include a paucity of sufficiently strenuous activity among older men or reduced responsiveness to typically weight-bearing activities.

We showed that greater time spent in MVPA was association with higher bone strength at both the distal radius and tibia. While modest, this association suggests that maintenance of MVPA is positively associated with bone strength, with minimal time spent in vigorous activity. The relatively modest associations might be attributable poor discrimination of activity levels or loss of information using summary time variables. Contrary to our hypothesis that unloading affects bone, our analysis did not show that time in light activity vs. time in sedentary activity was related to bone strength. Previous studies have shown that prolonged bed rest in among healthy adults was associated with longitudinal changes in HR-pQCT parameters with declines in trabecular number observed among women [30] and declines in cortical thickness and density and increases in trabecular area and total diameter of the distal tibia among men [31]. Bed rest precludes both light activity and MVPA; hence its effects may be attributable to global lack of activity. One study among adolescents has shown that sedentary time was not independently related to HR-pQCT parameters [32]. A cross-sectional population-based study using NHANES data showed that MVPA were both related to BMD among men, whereas time in sedentary behavior was not related to BMD [33].

Our findings concerning PA and bone strength support previous findings which related PA and fracture outcomes. In particular, Cauley et al. showed that higher TEE and active energy expenditure (i.e. energy spent in MVPA) were both associated with a lower risk of fracture among older men in the MrOS cohort [34]. This previous study also found an association between greater sedentary time and higher fracture risk which does not appear to be mediated by the bone strength measures of the present study. It is possible that there are subtle alterations in bone strength due to material properties not captured by HR-pQCT [35]. The association might also be mediated by other non-BMD risk factors, such as fall risk. In order to relate our study findings to fracture outcomes we note Samelson et al. performed a meta-analysis of multiple cohorts and found that each standard deviation decrease in failure load of the distal tibia was associated with an 2.4-fold increase in fracture risk [36]. Our results together with those of Samelson et al. suggest there is an estimated 20% increased risk in fracture per 1 SD decrease in mean TEE over 7 years.

This study has several strengths in that it was a large well-characterized cohort of older men and included repeat objective measures of PA to enable better categorization of habitual activity over a period of time likely to have some biological effect. We also assessed time dependent effects by considering both historical and concurrent objective PA measures. The study outcome measures were all based on high-resolution imaging, with the ability to differentiate cortical and trabecular compartmental vBMD. Our main outcome measures, HR-pQCT failure load of the distal limbs, are novel risk factors for osteoporotic fractures with a gradient of risk that is higher than for DXA areal BMD.

The main study limitation is the cross-sectional design. The cohort was comprised of generally healthy, mostly white, community-dwelling men and results may not be generalizable to women, minorities, those who are not community-dwelling or those with severely limited mobility. Biases related to selective survival are applicable in this older population. In addition, there was also information missing at each follow-up whereby those at greatest risk of adverse events were less likely to attend visits or have the relevant tests. Our main exposure variable was TEE which includes a wide variety of activity (regardless of weight bearing status) and hence is not a bone specific measure. Counts within a given range of force due to physical activity are not available in the present data. Use of an armband to measure overall physical activity may well underestimate more bone specific forces experienced by the tibia, while providing better estimates of upper-body movement and activity. We also note that the use of an activity monitor might impact activity levels due to the Hawthorne effect. Few studies have validated the use of activity monitors among the elderly. There are significant challenges relating to the differentiation of light and moderate activity among community-dwelling older adults.

In summary, we found that MVPA and TEE sustained over a 7-year period is modestly associated with bone area and strength among older men with slightly larger effect sizes at the tibia vs. the radius. Given the increasing risk of osteoporotic fracture with advancing age in men, older men should be counseled to maintain levels of MVPA.

Declaration of competing interest

Dr. Langsetmo reports grants from Abbott and Merck outside the submitted work; Dr. Burghardt reports grants from Ultragenex outside the submitted work; Dr. Schousboe reports grants from Merck outside the submitted work; Dr. Cawthon reports grants from Nestle and Abbott outside the submitted work; Dr. Orwoll reports consultation with Bayer and grants from Lilly and Mereo outside the submitted work; Dr. Ensrud reports grants from Merck outside the submitted work; Dr. Cauley and

Dr. Lane have no disclosures.

Acknowledgments

The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health funding. The following institutes provide support: the National Institute on Aging (NIA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Center for Advancing Translational Sciences (NCATS), and NIH Roadmap for Medical Research under the following grant numbers: U01 AG027810, U01 AG042124, U01 AG042139, U01 AG042140, U01 AG042143, U01 AG042145, U01 AG042168, U01 AR066160, and UL1 TR000128.

This manuscript is the result of work supported with resources and use of facilities of the Minneapolis VA Health Care System. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

Authors' roles

Study design/conduct and data collection: KEE, PMC, JAC, ESO; data analysis: LL and AJB; data interpretation: LL, AJB, JTS, PMC, JAC, NEL, ESO, KEE; drafting manuscript: LL; revising manuscript content and approval of final version: AJB, JTS, PMC, JAC, NEL, ESO, KEE.

LL and AJB take responsibility for the integrity of the data analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2019.115198.

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