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Weight Loss in Men in Late Life and Bone Strength and Microarchitecture: A Prospective Study

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Abstract

Purpose—To determine associations of weight loss with bone strength and microarchitecture.

Methods—We used data from 1723 community-dwelling men (mean age 84.5 years) who attended the MrOS study Year (Y) 14 exam and had high resolution peripheral quantitative computed tomography (HR-pQCT) scans at 1 skeletal sites (distal tibia, distal radius, or diaphyseal tibia). Weight change from Y7 to Y14 exams (mean 7.3 years between exams) was classified as moderate weight loss (loss ≥10%), mild weight loss (loss 5% to <10%), stable weight (<5% change) or weight gain (gain ≥5%). Mean HR-pQCT parameters (95%CI) were calculated by weight change category using linear regression models adjusted for age, race, site, health status, body mass index, limb length and physical activity. The primary outcome measure was estimated failure load.

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Conflict of Interest: Kristine Ensrud, Tien Vo, Andrew Burghardt, John Schousboe, Jane Cauley, Brent Taylor, Andrew Hoffman, Eric Orwoll, Nancy Lane, and Lisa Langsetmo declare that they have no conflict of interest.

Results—There was a non-linear association of weight change with failure load at each skeletal site with different associations for weight loss vs. weight gain ($p < 0.03$). Failure load and total bone mineral density (BMD) at distal sites were lower with greater weight loss with 7.0–7.6% lower failure loads and 4.3–5.8% lower BMDs among men with moderate weight loss compared to those with stable weight ($p < 0.01$, both comparisons). Cortical, but not trabecular, BMDs at distal sites were lower with greater weight loss. Greater weight loss was associated with lower cortical thickness at all three skeletal sites.

Conclusion—Weight loss in men in late life is associated lower peripheral bone strength and total BMD with global measures reflecting cortical but not trabecular parameters.

Keywords

weight change; bone microarchitecture; HR-pQCT; men

INTRODUCTION

Prior epidemiologic studies including the Osteoporotic Fractures in Men (MrOS) study[1-5] that have measured concurrent changes in weight and areal hip bone mineral density (BMD) have reported higher rates of bone loss among older adults losing weight. While measurement of areal BMD with dual energy x-ray absorptiometry (DXA) provides good precision and reproducibility and is available in clinical practice settings, DXA does not offer measures of compartment-specific BMD or bone microarchitecture.

The advent of high-resolution peripheral quantitative computed tomography (HRpQCT) has allowed characterization of cortical and trabecular microarchitecture and compartment-specific BMD at skeletal sites in the extremities such as the distal radius and tibia.[6] In addition, HRpQCT images can be used in a finite element analysis, a biomechanical computation method that yields loading scenario-specific, image-based estimates of bone strength such as the ultimate force required to fracture upon a certain type of fall[7,8] to virtually obtain estimates of bone strength. Declines in cortical and trabecular BMD with deterioration of microarchitecture at the distal radius and tibia have been observed after marked weight loss following Roux-en-Y gastric bypass in obese younger adults compared with obese nonsurgical controls.[9] However, the effect of weight loss in late life on bone strength and microarchitectural parameters is uncertain.

Our aim was to determine the associations of weight change with bone strength, compartmental BMD and microarchitecture using data from 1723 men who attended the Year 14 exam of the MrOS study and had high resolution peripheral quantitative computed tomography (HR-pQCT) scans of the distal tibia, distal radius, or diaphyseal tibia.

METHODS

Study Population

A total of 5,994 community-dwelling men 65 years old were enrolled from 2000 to 2002 in the prospective MrOS study.[10] Participants were recruited from population-based listings in six regions of the United States.[11] Individuals with a history of bilateral hip

replacement or the inability to walk without the assistance of another person were not eligible to participate. The institutional review board at each participating institution approved the study protocol and written informed consent was obtained from all participants. This analysis is limited to 1,723 men who completed both a clinic visit 3 (Year 7 (Y7) examination) and clinic visit 4 (Year 14 (Y14) examination), had body weight measured at both examinations, and had HR-pQCT scans at the Y14 examination completed for at least one of three skeletal sites (Figure 1).

Measurement of Weight Change

Body weight (indoor clothing, without shoes) was recorded with a scale (calibrated every month) at both Y7 and Y14 examinations (mean (SD) 7.3 (0.5) years between examinations). Weight change was calculated by subtracting Y7 weight from Y14 weight and expressed as a percentage of the Y7 value. For primary analyses, weight change was categorized as moderate weight loss (loss $\geq 10\%$), mild weight loss (loss 5% to $<10\%$), stable weight ($<5\%$ loss or gain) or weight gain (gain $\geq 5\%$) based on standard cut-offs for clinically relevant weight changes in older adults and availability of sufficient numbers of participants in each category.[12,13]

Measurement of HR-pQCT Parameters

HR-pQCT scans were completed using Scanco XtremeCT II machines (Scanco Medical AG, Brüttisellen, Switzerland), which have nominal voxel size of $61\mu\text{m}$. Operators were centrally trained and certified to perform the imaging protocol, including an online scan positioning operator calibration procedure that has been shown to reduce inter-operator measurement error for bone outcomes by approximately 50%.[14] Operators acquired scans of the distal radius (9 mm from the articular surface), distal tibia (22 mm from the articular surface), and diaphyseal tibia (centered at 30% of tibial length, as externally measured from tibial plateau proximally to the tibial malleolus at the distal end).[15] The radius from the non-dominant arm and the tibia from the ipsilateral leg were scanned except in the case of prior fracture, metal shrapnel or implant, or recent complete non-weight bearing period >6 weeks during the previous 12 months. Machines were calibrated prior to being used in the present study, and a single cross-calibration density phantom was circulated among the study sites. The between site calibration coefficients were all $<0.6\%$, and therefore pooled data was used without transformations.[16] The standard local density phantom was scanned on a daily basis to monitor for values that fall outside of the nominal range (8 mg HA/cm^3). Centralized quality assurance (QA) and standard analysis of all image data, including micro finite element analysis (μFEA), was performed.

A central observer read all images for motion artifacts and used an established semi-quantitative 5-point grading system (1=superior, 5=poor) to score image quality. Images with 4 or 5 were deemed to be of insufficient quality and were excluded from the analytic data set (97% of scans image grade ≥ 3).[17] A fully automated analysis pipeline was developed to segment the radius and tibia for quantification of bone density and structure. [18] For this study an automated QA algorithm was developed to detect bone segmentation errors. The slice-wise variation in total cross-sectional area was measured to identify contours that failed to locate the outer cortical perimeter of the radius or tibia; cases with an

absolute slice-wise difference of 2 mm² at the diaphysis, and 4 mm² at the distal sites, were visually reviewed and manually corrected, as needed. Observed failure rates were <2% and <6%, for diaphyseal and distal scans, respectively.

Volumetric BMD and cross sectional area of the total, cortical, and trabecular compartments were measured. Cortical porosity and thickness, and trabecular thickness, separation and number were calculated directly.[19,20] 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%.[21] The cortical load fraction was calculated as the integral force on cortical bone elements, divided by the total reaction force.[22]

All participants with outliers (difference from mean >3 SDs) were reviewed and those with abnormal anatomic findings at a given skeletal site that precluded analysis (e.g. evidence of prior unreported fracture, osteolytic lesion, ossification injury, severe inflammatory arthritis) were excluded from the analysis at that skeletal site (n=6 at distal tibia, 17 at distal radius, 0 at diaphyseal tibia) (Figure 1).

Other Measurements

At the Y7 examination, participants completed a questionnaire and were interviewed and asked about health status (i.e. overall health compared to people of their own age (excellent, good, fair, poor, or very poor)). Physical activity was assessed using the Physical Activity Scale for the Elderly (PASE).[23] Weight and height (Harpender stadiometer) measurements were used to calculate body mass index (BMI, kg/m²). Information regarding date of birth and race/ethnicity was collected at the baseline examination. After the baseline examination, surviving participants were contacted every 4 months about clinical fractures. Over 99% of these follow-up contacts were completed. Fractures were confirmed by review of radiographic reports.

Statistical Analysis

Differences in characteristics of the 1,723 men included in the analytic cohort at the Y7 exam across weight change categories were compared using chi-squared tests for categorical variables and ANOVA for continuous variables.

We used restricted cubic splines to assess whether the associations between weight change and estimated failure load at each skeletal site (primary outcome) were nonlinear. To allow for flexibility in model fit, we chose a spline model with 3 knots placed at the 25th, 50th and 75th percentiles of percent weight change. We then plotted the spline curve and 95% confidence intervals for estimated failure load at each of the 3 skeletal sites versus percent weight change truncating the upper and lower 5% tails due to sparse data. These graphs suggested the presence of a nonlinear association between weight change and estimated failure load with attenuation of the relationship for those with weight gain, confirming that it was appropriate to express weight change as a categorical variable and that the comparisons of weight change with stable weight might depend on whether there was weight loss or weight gain.

To examine the association of weight change with each HR-pQCT parameter, linear regression models were used to calculate adjusted least square means (95% confidence interval [CI]) HR-pQCT parameters by weight change category. Initial models were adjusted for age, race, and study enrollment site; then further adjusted for health status, BMI, limb length and physical activity. To determine if there was evidence that association of weight change with the primary HR-pQCT outcome differed by age or BMI, we also performed analyses testing for interactions between weight change and age and weight change and BMI for prediction of estimated failure load at each of the three skeletal sites. In these analyses, weight change was expressed as a categorical and continuous variable.

Using the Cohen approach[24] for calculating power for the multivariable regression analyses predicting estimated failure load and assuming an alpha significance level of 0.05, a sample size of 1182 participants was needed to detect a small effect size of 0.01. Statistical analysis was performed using SAS (version 9.4; SAS Institute, Cary, NC, USA) and Stata (version 14, Stata Corp, College Station, Texas, USA).

RESULTS

Among the 1,723 men who comprised the analytical cohort, mean (SD) participant age was 77.2 (4.2) years at the Y7 exam (84.5 (4.2) years at Y14 exam) and 90.7% were Caucasian. On average, those in the cohort lost weight with mean (SD) percent weight change of -3.5% (6.7%) between Y7 and Y14. A total of 257 men (14.9%) had moderate weight loss, 410 (23.8%) had mild weight loss, 911 (52.9%) had stable weight and 145 (8.4%) had weight gain. Characteristics of the cohort overall and by weight change category are shown in Table 1.

The estimated slope relating weight change and failure load among those with weight loss was significantly different from the slope among those with weight gain ($p < 0.03$ at all skeletal sites) assuming a linear model with a change point of zero. A non-linear association between weight change and estimated failure load at each site was also observed in analyses using restricted cubic spline models (Figure 2).

Distal Tibia

Estimated failure load and total (integral) BMD at the distal tibia were lower in a graded manner with increasing weight loss in multivariable models with a 7.6% lower failure load and 5.8% lower BMD among those with moderate weight loss compared to those with stable weight ($p < 0.001$ for both comparisons) (Table 2). Weight gain compared with stable weight was associated with higher distal tibia total BMD extending the graded pattern for weight change categories, but weight gain compared with stable weight was not associated with higher distal tibia failure load (Figure 2A). Cortical thickness, cortical BMD and estimated cortical proximal load fraction were also lower in a graded manner with increasing weight loss with a 8.0% lower thickness, 4.3% lower BMD and 4.8% lower proximal load fraction among those with moderate weight loss compared to those with stable weight ($p < 0.001$ for all comparisons). There were no significant differences in cortical porosity or any of the trabecular parameters across weight change categories.

Distal Radius

Estimated failure load and total BMD at the distal radius were lower in a graded manner with increasing weight loss in multivariable models with a 7.0% lower failure load and 5.3% lower BMD among those with moderate weight loss compared to those with stable weight ($p < 0.01$ for both comparisons) (Table 3). The graded pattern observed for weight loss categories extended to men with weight gain for distal radius total BMD, but did not extend for failure load (Figure 2B). Similar to results for the distal tibia, weight gain compared with stable weight was not associated with a higher distal radius failure load. Cortical BMD and cortical thickness were also lower in a graded manner among those with weight-loss compared to those with stable weight with 5.4% lower thickness and 1.9% lower BMD among those with moderate weight loss compared to those with stable weight ($p < 0.01$ for all comparisons). There were no significant differences in cortical porosity across weight change categories. After adjustment for age, race, and study enrollment site, estimated proximal cortical load fraction significantly varied across weight change categories with lower cortical load fraction among men with weight loss, but these differences were not significant ($p = 0.08$) in the multivariable model. In addition, trabecular number and trabecular bone volume fraction (but not trabecular thickness or trabecular BMD) significantly varied by weight change category in multivariable models with lower values among men with weight loss.

Diaphyseal Tibia

There were no significant differences in estimated failure load or total BMD at the diaphyseal tibia across weight change categories (Table 4), but the spline curve relating percent weight change versus failure load suggested a pattern similar to that observed at the distal skeletal sites (Figure 2C). Cortical thickness was 3.2% lower among men with moderate weight loss compared to those with stable weight ($p < 0.01$). After adjustment for age, race, and study enrollment site, cortical porosity significantly varied across weight change categories with greater porosity among men with weight loss, but these differences were not significant ($p = 0.09$) in the multivariable model. There were no significant differences in any other diaphyseal tibia HR-pQCT parameters by weight change category.

Additional Analyses

We found no significant interactions between weight change and age (p for interaction terms 0.18) or weight change and BMI (p for interaction terms 0.48) for prediction of estimated failure load at any of the three skeletal sites (data not shown).

DISCUSSION

In this prospective study of community-dwelling older men, we observed a non-linear association between weight change and bone strength (as measured by FEA estimated failure load at the distal tibia and radius and diaphyseal tibia). Bone strength, total BMD and cortical BMD at the distal skeletal sites were significantly lower among men with weight loss compared to those with stable weight, but men with weight gain did not have higher bone strength despite a total BMD that was similar to or higher than that among those with stable weight. These findings did not vary by age or body mass index. In addition, weight

loss was associated with lower cortical thickness across all three skeletal sites, but was not consistently associated with trabecular parameters at any site.

Our results indicate that decline in body weight commonly observed with advancing age[25] is detrimental to bone strength. This finding is in agreement with those of prospective studies (including investigations from this cohort) that have reported associations of weight loss with higher rates of hip bone loss[1,3–5] (measured using dual x-ray absorptiometry) and increased risks of hip fracture.[2,12,26] We observed a consistent adverse effect of weight loss on bone strength across distal weight bearing and non-weight bearing sites suggesting that factors in addition to mechanical unloading of the skeleton such as hormonal changes and loss of muscle mass with weight loss likely underlie these associations.[27] However, our results also suggest that weight gain in aged populations is not accompanied by a commensurate increase in bone strength. While previous studies have found lower rates of hip bone loss (measured using dual x-ray absorptiometry) among older adults with weight gain compared to those with stable weight[2,3], prior investigations have also noted similar risks of hip fracture in individuals with weight gain and those with stable weight.[2,12] Older adults who gain weight are more likely to add fat mass rather than lean mass[28], but most studies suggest that lean tissue mass has a stronger protective effect on bone compared with fat mass. A previous case-control study of 63 obese postmenopausal women (mean age 69 years) and 126 age-matched normal weight postmenopausal women reported a positive effect of obesity on estimated failure load at the distal tibia and radius, but noted that the higher bone strength among obese women was lower relative to the excess of BMI (especially fat mass) among obese women compared with normal weight controls.[29]

Total BMD at the distal tibia and radius in this cohort of older men was lower with increasing degree of weight loss and men with weight gain had a total BMD that was similar to or higher than that among those with stable weight. A prospective study[30] using data from 1364 men and women (mean age 70 years, range 48–95 years) participants in the Framingham Study reported an association of greater weight loss with lower total BMD at the distal tibia that was similar among obese and non-obese participants. However, this investigation did not examine this association at other skeletal sites or evaluate the relationship of weight loss with failure load. A small longitudinal study[9] of younger adults with severe obesity (30 undergoing Roux-en-Y gastric bypass surgery and 20 nonsurgical controls) found a 9–10% lower estimated failure load and a 9% lower total BMD at both the distal radius and tibia after gastric bypass (that resulted in marked weight loss of 30% of baseline weight) as compared with controls. Of note, the observed declines in these parameters in the first 12 months after bypass were matched or exceeded by the declines in the subsequent 12 to 24 month period despite a plateauing of weight loss and weight stability in the second year.

We found that greater degrees of weight loss were associated with lower cortical thickness across the three skeletal sites and lower cortical BMD at distal sites. However, cortical porosity did not significantly differ across weight change categories. Longitudinal studies have reported associations of advancing age with increases in cortical porosity and declines in cortical BMD and thickness among men and women, though increases in cortical porosity are smaller in men compared with women.[31,32] It may be that weight loss does not

contribute to the age-related increase in cortical porosity or that we failed to detect a true association due to limitations of HR-pQCT scanners in the accurate detection of all cortical pores, especially those with a diameter $<100\text{ }\mu\text{m}$. [33] Thus, an increase in cortical porosity might be reflected by the apparent reduction in cortical BMD. Furthermore, our cross-sectional study cannot determine whether an increase in cortical porosity results in a shift of the cortical-trabecular boundary due to trabecularization, thus resulting in less consolidated and thinner cortex. The Framingham study [30] that examined the association of weight loss on bone microarchitecture at the distal tibia in obese and non-obese individuals reported that greater weight loss was associated with lower cortical BMD and lower cortical thickness among both groups, but the association of greater weight loss with greater cortical porosity was only observed among non-obese individuals. Cortical BMD was reduced and cortical porosity was greater among obese younger adults experiencing marked weight loss after gastric bypass compared with obese nonsurgical controls. [9]

There were no differences in trabecular BMD or other trabecular parameters across weight change categories in our study, except for slightly lower trabecular number and trabecular bone volume fraction at the distal radius among men with weight loss. Thus, the effect of weight loss in late life on bone microarchitecture of the peripheral skeleton, in which the bone marrow compartment is replaced with fat resulting in very little trabecular bone remodeling, may be predominantly on the cortical compartment. Longitudinal studies examining the effect of advancing age on changes in bone microarchitecture have reported a dominance of cortical over trabecular bone loss in both sexes. [31,32] In the Framingham study, weight loss was associated with lower trabecular number (but not related to trabecular BMD) at the distal tibia. [30] In contrast, declines in trabecular BMD at the distal tibia and radius among younger obese adults were greater after gastric bypass compared with that among nonsurgical controls. [9]

This study has several strengths. It was comprised of a large cohort of older men with repeated objective measures of body weight. Centralized quality assurance and standard analysis of HR-pQCT image data were performed. However, this study also has several limitations. The cohort was predominantly Caucasian community-dwelling men, so results may not be generalizable to other populations. Multiple statistical comparisons were performed and some of the observed associations may be explained by chance alone. On the other hand, our findings regarding associations of weight loss with failure load and BMD were consistent across the distal skeletal sites suggesting that these associations are not spurious. We performed longitudinal measurements of body weight, but the bone strength and microarchitecture parameters were measured at a single point in time. Thus, our study may miss associations that are only apparent when considering change within individuals. The weight gain group comprised less than 9% of the overall cohort and average weight gain in this group was modest in magnitude. The body weight measurements were spaced an average of 7 years apart and the trajectory of the weight change between these two time points cannot be examined. Future research is needed to explore the relative contributions of changes in fat and lean mass to measures of peripheral bone strength, compartmental BMD and microarchitecture. Finally, our study has an observational design and the possibility of residual confounding cannot be eliminated.

In conclusion, weight loss among community-dwelling men in late life is associated with detrimental effects on bone strength and total and cortical BMD at distal skeletal sites and detrimental effects on cortical thickness at distal and proximal sites. Weight gain in late life is not associated with a commensurate increase in bone strength. Future studies should measure concurrent changes in body weight and parameters of bone strength, compartmental BMD and microarchitecture and evaluate potential causal pathways underlying the association.

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References

1. Dennison E, Eastell R, Fall CH, Kellingray S, Wood PJ, Cooper C. Determinants of bone loss in elderly men and women: a prospective population-based study. *Osteoporos Int.* 1999; 10:384–91. [PubMed: 10591836]
2. Ensrud KE, Ewing SK, Stone KL, Cauley JA, Bowman PJ, Cummings SR. Intentional and unintentional weight loss increase bone loss and hip fracture risk in older women. *J Am Geriatr Soc.* 2003; 51:1740–1747. [PubMed: 14687352]
3. Ensrud KE, Fullman RL, Barrett-Connor E, Cauley JA, Stefanick ML, Fink HA, Lewis CE, Orwoll E. Voluntary weight reduction in older men increases hip bone loss: the osteoporotic fractures in men study. *J Clin Endocrinol Metab.* 2005; 90:1998–2004. [PubMed: 15671096]
4. Hannan MT, Felson DT, Dawson-Hughes B, Tucker KL, Cupples LA, Wilson PW, Kiel DP. Risk factors for longitudinal bone loss in elderly men and women: the Framingham Osteoporosis Study. *J Bone Miner Res.* 2000; 15:710–720. [PubMed: 10780863]
5. Knoke JD, Barrett-Connor E. Weight loss: a determinant of hip bone loss in older men and women. The Rancho Bernardo Study. *Am J Epidemiol.* 2003; 158:1132–38. [PubMed: 14652297]
6. Patsch JM, Burghardt AJ, Kazakia G, Majumdar S. Noninvasive imaging of bone microarchitecture. *Ann N Y Acad Sci.* 2011; 1240:77–87. [PubMed: 22172043]
7. Liu XS, Zhang XH, Sekhon KK, Adams MF, McMahon DJ, Bilezikian JP, Shane E, Guo XE. High-resolution peripheral quantitative computed tomography can assess microstructural and mechanical properties of human distal tibial bone. *J Bone Miner Res.* 2010; 25:746–56. [PubMed: 19775199]
8. MacNeil JA, Boyd SK. Bone strength at the distal radius can be estimated from high-resolution peripheral quantitative computed tomography and the finite element method. *Bone.* 2008; 42:1203–13. [PubMed: 18358799]
9. Yu EW, Bouxsein ML, Putman MS, Monis EL, Roy AE, Pratt JS, Butsch WS, Finkelstein JS. Two-year changes in bone density after Roux-en-Y gastric bypass surgery. *J Clin Endocrinol Metab.* 2015; 100:1452–59. [PubMed: 25646793]
10. Orwoll E, Blank JB, Barrett-Connor E, Cauley J, Cummings S, Ensrud K, Lewis C, Cawthon PM, Marcus R, Marshall LM, McGowan J, Phipps K, Sherman S, Stefanick ML, Stone K. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study--a large observational study of the determinants of fracture in older men. *Contemp Clin Trials.* 2005; 26:569–85. [PubMed: 16084776]

11. Blank JB, Cawthon PM, Carrion-Petersen ML, Harper L, Johnson JP, Mitson E, Delay RR. Overview of recruitment for the Osteoporotic Fractures in Men study (MrOS). *Contemp Clin Trials*. 2005; 26:557–68. [PubMed: 16085466]
12. Ensrud KE, Harrison SL, Cauley JA, Langsetmo L, Schousboe JT, Kado DM, Gourlay ML, Lyons JG, Fredman L, Napoli N, Crandall CJ, Lewis CE, Orwoll ES, Stefanick ML, Cawthon PM. Impact of competing risk of mortality on association of weight loss with risk of central body fractures in older men: a prospective cohort study. *J Bone Miner Res*. 2017; 32:624–32. [PubMed: 27739103]
13. Newman AB, Yanez D, Harris T, Duxbury A, Enright PL, Fried LP. Weight change in old age and its association with mortality. *J Am Geriatr Soc*. 2001; 49:1309–18. [PubMed: 11890489]
14. Bonaretti S, Vilayphiou N, Chan CM, Yu A, Nishiyama K, Liu D, Boutroy S, Ghasem-Zadeh A, Boyd SK, Chapurlat R, McKay H, Shane E, Bouxsein ML, Black DM, Majumdar S, Orwoll ES, Lang TF, Khosla S, Burghardt AJ. Operator variability in scan positioning is a major component of HR-pQCT precision error and is reduced by standardized training. *Osteoporos Int*. 2017; 28:245–57. [PubMed: 27475931]
15. Bonaretti S, Majumdar S, Lang TF, Khosla S, Burghardt AJ. The comparability of HR-pQCT bone measurements is improved by scanning anatomically standardized regions. *Osteoporos Int*. 2017; 28:2115–28. [PubMed: 28391447]
16. Burghardt AJ, Pialat JB, Kazakia GJ, Boutroy S, Engelke K, Patsch JM, Valentinitich A, Liu D, Szabo E, Bogado CE, Zanchetta MB, McKay HA, Shane E, Boyd SK, Bouxsein ML, Chapurlat R, Khosla S, Majumdar S. Multicenter precision of cortical and trabecular bone quality measures assessed by high-resolution peripheral quantitative computed tomography. *J Bone Miner Res*. 2013; 28:524–36. [PubMed: 23074145]
17. Pialat JB, Burghardt AJ, Sode M, Link TM, Majumdar S. Visual grading of motion induced image degradation in high resolution peripheral computed tomography: impact of image quality on measures of bone density and micro-architecture. *Bone*. 2012; 50:111–18. [PubMed: 22019605]
18. Burghardt AJ, Buie HR, Laib A, Majumdar S, Boyd SK. Reproducibility of direct quantitative measures of cortical bone microarchitecture of the distal radius and tibia by HR-pQCT. *Bone*. 2010; 47:519–28. [PubMed: 20561906]
19. Hildebrand T, Laib A, Muller R, Dequeker J, Rueggsegger P. Direct three-dimensional morphometric analysis of human cancellous bone: microstructural data from spine, femur, iliac crest, and calcaneus. *J Bone Miner Res*. 1999; 14:1167–74. [PubMed: 10404017]
20. Manske SL, Zhu Y, Sandino C, Boyd SK. Human trabecular bone microarchitecture can be assessed independently of density with second generation HR-pQCT. *Bone*. 2015; 79:213–21. [PubMed: 26079995]
21. Mueller TL, Christen D, Sandercott S, Boyd SK, van RB, Eckstein F, Lochmuller EM, Muller R, van Lenthe GH. Computational finite element bone mechanics accurately predicts mechanical competence in the human radius of an elderly population. *Bone*. 2011; 48:1232–38. [PubMed: 21376150]
22. MacNeil JA, Boyd SK. Load distribution and the predictive power of morphological indices in the distal radius and tibia by high resolution peripheral quantitative computed tomography. *Bone*. 2007; 41:129–37. [PubMed: 17442649]
23. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol*. 1993; 46:153–62. [PubMed: 8437031]
24. Cohen, J. Statistical power analysis for the behavioral sciences. 2. Hillsdale, N.J.: L. Erlbaum Associates; 1988.
25. Williamson DF, Kahn HS, Remington PL, Anda RF. The 10-year incidence of overweight and major weight gain in US adults. *Arch Intern Med*. 1990; 150:665–72. [PubMed: 2310286]
26. Crandall CJ, Hovey KM, Cauley JA, Andrews CA, Curtis JR, Wactawski-Wende J, Wright NC, Li W, LeBoff MS. Wrist fracture and risk of subsequent fracture: findings from the Women's Health Initiative study. *J Bone Miner Res*. 2015; 30:2086–95. [PubMed: 25990562]
27. Schafer AL. Decline in bone mass during weight loss: a cause for concern? *J Bone Miner Res*. 2016; 31:36–39. [PubMed: 26595270]

28. Lee CG, Boyko EJ, Nielson CM, Stefanick ML, Bauer DC, Hoffman AR, Dam TT, Lapidus JA, Cawthon PM, Ensrud KE, Orwoll ES. Mortality risk in older men associated with changes in weight, lean mass, and fat mass. *J Am Geriatr Soc.* 2011; 59:233–40. [PubMed: 21288234]
29. Sornay-Rendu E, Boutroy S, Vilaythiou N, Claustrat B, Chapurlat RD. In obese postmenopausal women, bone microarchitecture and strength are not commensurate to greater body weight: the Os des Femmes de Lyon (OFELY) study. *J Bone Miner Res.* 2013; 28:1679–87. [PubMed: 23371055]
30. Samelson E, Kiel D, Broe K, Xu H, Yang L, McLean R, Sahni S, Hannan M, Boussein M, Liu C-T. Adverse effects of weight loss on bone microarchitecture in obese and non-obese older adults: the Framingham Study. *J Bone Miner Res.* 2017; 32(Suppl 1) [Accessed 10-24-2017] Available at <http://www.asbmr.org/education/AbstractDetail?aid=896de97f-5da8-4680-978e-1e170f9e0b6c>.
31. Burt LA, Hanley DA, Boyd SK. Cross-sectional versus longitudinal change in a prospective HR-pQCT study. *J Bone Miner Res.* 2017; 32:1505–13. [PubMed: 28294405]
32. Shanbhogue VV, Brixen K, Hansen S. Age- and sex-related changes in bone microarchitecture and estimated strength: a three-year prospective study using HRpQCT. *J Bone Miner Res.* 2016; 31:1541–49. [PubMed: 26896351]
33. Cooper DM, Kawalilak CE, Harrison K, Johnston BD, Johnston JD. Cortical bone porosity: what is it, why is it important, and how can we detect it? *Curr Osteoporos Rep.* 2016; 14:187–98. [PubMed: 27623679]

Fig 1.
Participant Flow

Fig 2. Restricted Cubic Spline Plot of Estimated Failure Load at (a) Distal Tibia by Percent Weight Change, (b) Distal Radius by Percent Weight Change and (c) Diaphyseal Tibia by Percent Weight Change

Characteristics of 1723 Men at Year 7 Examination Overall and by Category of Weight Change

Table 1

Characteristic	Overall(n=1723)	Weight Loss 10%(n=257)	Weight Loss 5% to <10%(n=410)	Stable Weight(Loss or Gain <5%)(n=911)	Weight Gain 5%(n=145)	P-value*
Age, years, mean (SD)	77.2 (4.2)	78.0 (4.4)	77.3 (4.2)	76.9 (4.1)	77.2 (4.0)	<0.001
Caucasian, n (%)	1562 (90.7)	229 (89.1)	364 (88.8)	837 (91.9)	132 (91.0)	0.26
Health status, fair/poor/very poor [†] , n (%)	140 (8.1)	36 (14.0)	25 (6.1)	64 (7.0)	15 (10.3)	<0.001
BMI, kg/m ² , mean (SD)	27.3 (3.6)	28.4 (4.1)	27.4 (3.4)	26.9 (3.4)	26.7 (3.4)	<0.001
PASE score, mean (SD)	147.5 (66.5)	138.3 (68.3)	142.8 (64.8)	152.3 (66.9)	146.2 (64.2)	0.008
Femoral neck BMD [‡] , g/cm ² , mean (SD)	0.785 (0.128)	0.789 (0.145)	0.773 (0.117)	0.790 (0.127)	0.784 (0.128)	0.16
Femoral neck BMD T-score [‡] , mean (SD)	0.61 (1.07)	0.58 (1.21)	0.71 (0.98)	0.57 (1.06)	0.61 (1.07)	0.16
Tibia length§, mean (SD)	404.4 (24.8)	404.9 (24.5)	405.1 (23.9)	404.2 (24.9)	402.6 (26.7)	0.74
Ulnar length (distal radius) [¶] , mean (SD)	286.3 (14.8)	285.8 (16.0)	287.3 (13.6)	286.2 (15.0)	285.0 (14.5)	0.34
Gait speed, m/s, mean (SD)	1.20 (0.20)	1.15 (0.24)	1.19 (0.20)	1.23 (0.20)	1.18 (0.20)	<0.001
Grip strength, kg, mean (SD)	38.4 (7.9)	37.2 (8.5)	38.3 (8.1)	39.2 (7.5)	36.4 (7.7)	<0.001
Clinical fractures between baseline and Year 7, n (%)	136 (7.9)	29 (11.3)	25 (6.1)	71 (7.8)	11 (7.6)	0.12

Abbreviations: BMI, body mass index; PASE, Physical Activity Scale for the Elderly; BMD, bone mineral density

* ANOVA for continuous variables and chi-square test for categorical variables

[†] Overall n=1721

[‡] Overall n=1693 § Overall n=1696

[¶] Overall n=1699

Table 2

Mean Compartmental BMD and Bone Microarchitecture Parameters (95% CI) at Distal Tibia According to Weight Change Category (N=1648)

	Weight Loss 10%(n=247)	Weight Loss 5% to <10%(n=394)	Stable Weight (Loss or Gain <5%)(n=872)	Weight Gain 5%(n=135)	P-value
Base model [*]					
FEA estimated failure load, N	12914(12555, 13273)	13460(13176, 13743)	13694(13503, 13886)	13329(12845, 13814)	0.002
FEA proximal cortical load fraction, %	59.9 (58.6, 61.2)	62.1 (61.0, 63.1)	62.9 (62.2, 63.6)	65.1 (63.4, 66.9)	<0.001
Integral BMD, mg/cm ³	267.6 (260.8, 274.4)	276.6 (271.2, 281.9)	282.4 (278.8, 286.0)	284.3 (275.2, 293.5)	0.001
Total area, mm ²	903.6 (886.4, 920.7)	898.6 (885.1, 912.1)	891.7 (882.6, 900.8)	869.7 (846.6, 892.8)	0.11
Trabecular BMD, mg/cm ³	183.9 (179.2, 188.6)	185.0 (181.3, 188.7)	185.5 (183.0, 188.0)	180.7 (174.4, 187.1)	0.57
Trabecular bone volume fraction, mm ³	0.267 (0.260, 0.273)	0.268 (0.263, 0.273)	0.269 (0.266, 0.273)	0.262 (0.254, 0.271)	0.49
Trabecular number, mm ⁻¹	1.35 (1.33, 1.38)	1.34 (1.32, 1.37)	1.35 (1.33, 1.36)	1.34 (1.30, 1.37)	0.89
Trabecular thickness, mm	0.273 (0.270, 0.276)	0.274 (0.272, 0.276)	0.272 (0.270, 0.273)	0.270 (0.267, 0.274)	0.26
Cortical BMD, mg/cm ³	752.1 (742.6, 761.6)	770.8 (763.2, 778.3)	785.3 (780.2, 790.4)	799.4 (786.5, 812.2)	<0.001
Cortical thickness, mm	1.39 (1.35, 1.43)	1.46 (1.43, 1.49)	1.49 (1.46, 1.51)	1.51 (1.45, 1.56)	<0.001
Cortical porosity, %	4.38 (4.18, 4.59)	4.32 (4.16, 4.48)	4.27 (4.16, 4.38)	4.07 (3.80, 4.36)	0.35
Multivariable model [†]					
FEA estimated failure load, N	12778(12426, 13131)	13378(13102, 13654)	13745(13559, 13931)	13489(13018, 13959)	<0.001
FEA proximal cortical load fraction, %	60.0 (58.8, 61.3)	62.1 (61.1, 63.1)	62.9 (62.3, 63.6)	65.1 (63.4, 66.7)	<0.001
Integral BMD, mg/cm ³	267.2 (260.6, 273.7)	276.1 (271.0, 281.2)	282.6 (279.2, 286.1)	285.0 (276.3, 293.7)	<0.001
Total area, mm ²	895.3 (880.9, 909.6)	894.1 (882.9, 905.3)	894.6 (887.0, 902.2)	878.9 (859.7, 898.1)	0.50
Trabecular BMD, mg/cm ³	183.2 (178.4, 187.9)	184.5 (180.8, 188.2)	185.8 (183.3, 188.3)	181.6 (175.2, 187.8)	0.55
Trabecular bone volume fraction, mm ³	0.266 (0.259, 0.272)	0.268 (0.263, 0.273)	0.270 (0.266, 0.273)	0.263 (0.255, 0.272)	0.46
Trabecular number, mm ⁻¹	1.34 (1.32, 1.37)	1.34 (1.32, 1.36)	1.35 (1.34, 1.37)	1.35 (1.31, 1.38)	0.80
Trabecular thickness, mm	0.273 (0.270, 0.275)	0.274 (0.272, 0.276)	0.272 (0.270, 0.273)	0.270 (0.266, 0.274)	0.23
Cortical BMD, mg/cm ³	752.9 (743.7, 762.1)	771.0 (763.7, 778.2)	785.2 (780.3, 790.1)	799.8 (787.4, 812.1)	<0.001
Cortical thickness, mm	1.38 (1.34, 1.42)	1.45 (1.42, 1.48)	1.49 (1.47, 1.51)	1.51 (1.46, 1.57)	<0.001
Cortical porosity, %	4.40 (4.19, 4.60)	4.33 (4.17, 4.50)	4.26 (4.15, 4.37)	4.06 (3.78, 4.34)	0.25

^{*} adjusted for age, race, and site[†] adjusted for age, race, site, health status, body mass index, limb length and physical activity

Table 3

Mean Compartmental BMD and Bone Microarchitecture Parameters (95% CI) at Distal Radius According to Weight Change Category (N=1638)

	Weight Loss 10%(n=243)	Weight Loss5% to <10%(n=382)	Stable Weight(Loss or Gain <5%)(n=872)	Weight Gain 5%(n=141)	P-value
Base model [*]					
FEA estimated failure load, N	4672 (4507, 4837)	4739 (4607, 4870)	4944 (4857, 5031)	4884 (4668, 5100)	0.009
FEA proximal cortical load fraction, %	75.5 (74.5, 76.5)	76.2 (75.4, 77.0)	76.7 (76.1, 77.2)	77.7 (76.4, 79.1)	0.05
Integral BMD, mg/cm ³	265.5 (257.9, 273.0)	267.9 (261.9, 274.0)	278.0 (274.0, 282.0)	280.5 (270.6, 290.4)	0.003
Total area, mm ²	398.7 (390.5, 407.0)	399.5 (392.9, 406.0)	396.5 (392.1, 400.8)	388.6 (377.7, 399.4)	0.38
Trabecular BMD, mg/cm ³	167.6 (162.7, 172.6)	167.3 (163.4, 171.3)	171.9 (169.3, 174.5)	170.4 (163.9, 176.9)	0.20
Trabecular bone volume fraction, mm ³	0.233 (0.225, 0.240)	0.232 (0.227, 0.238)	0.240 (0.236, 0.244)	0.238 (0.228, 0.247)	0.13
Trabecular number, mm ⁻¹	1.38 (1.35, 1.41)	1.39 (1.37, 1.41)	1.41 (1.40, 1.43)	1.41 (1.37, 1.44)	0.09
Trabecular thickness, mm	0.248 (0.246, 0.250)	0.246 (0.244, 0.248)	0.247 (0.246, 0.248)	0.248 (0.245, 0.251)	0.54
Cortical BMD, mg/cm ³	782.4 (774.1, 790.8)	789.3 (782.7, 796.0)	798.5 (794.1, 802.9)	806.0 (795.1, 817.0)	<0.001
Cortical thickness, mm	0.92 (0.89, 0.95)	0.93 (0.91, 0.96)	0.97 (0.95, 0.98)	0.98 (0.94, 1.01)	0.003
Cortical porosity, %	1.66 (1.56, 1.77)	1.55 (1.47, 1.63)	1.58 (1.53, 1.64)	1.62 (1.48, 1.75)	0.36
Multivariable model [†]					
FEA estimated failure load, N	4632 (4468, 4796)	4721 (4592, 4851)	4955 (4869, 5041)	4935 (4722, 5148)	<0.001
FEA proximal cortical load fraction, %	75.6 (74.6, 76.7)	76.3 (75.5, 77.1)	76.6 (76.1, 77.2)	77.7 (76.4, 79.0)	0.08
Integral BMD, mg/cm ³	264.3 (256.9, 271.8)	268.2 (262.4, 274.1)	278.2 (274.3, 282.1)	280.5 (270.8, 290.1)	0.001
Total area, mm ²	397.5 (390.1, 405.0)	397.3 (391.4, 403.2)	397.0 (393.1, 400.9)	393.2 (383.5, 402.9)	0.90
Trabecular BMD, mg/cm ³	166.3 (161.4, 171.3)	167.4 (163.5, 171.3)	172.2 (169.6, 174.8)	170.8 (164.4, 177.3)	0.09
Trabecular bone volume fraction, mm ³	0.231 (0.224, 0.238)	0.232 (0.227, 0.238)	0.240 (0.236, 0.244)	0.239 (0.229, 0.248)	0.05
Trabecular number, mm ⁻¹	1.37 (1.34, 1.40)	1.39 (1.37, 1.41)	1.42 (1.40, 1.43)	1.41 (1.38, 1.45)	0.007
Trabecular thickness, mm	0.248 (0.246, 0.250)	0.246 (0.244, 0.248)	0.247 (0.246, 0.248)	0.247 (0.244, 0.250)	0.59
Cortical BMD, mg/cm ³	783.3 (775.0, 791.6)	789.7 (783.1, 796.3)	798.3 (793.9, 802.6)	805.4 (794.6, 816.2)	0.002
Cortical thickness, mm	0.92 (0.89, 0.95)	0.93 (0.91, 0.96)	0.97 (0.95, 0.98)	0.98 (0.94, 1.01)	0.001
Cortical porosity, %	1.67 (1.56, 1.77)	1.55 (1.47, 1.63)	1.58 (1.53, 1.64)	1.61 (1.47, 1.74)	0.36

^{*} adjusted for age, race, and site[†] adjusted for age, race, site, health status, body mass index, limb length and physical activity

Table 4

Mean Compartmental BMD and Bone Microarchitecture Parameters (95% CI) at Diaphyseal Tibia According to Weight Change Category (N=1442)

	Weight Loss 10%(n=207)	Weight Loss 5% to <10%(n=345)	Stable Weight(Loss or Gain <5%)(n=772)	Weight Gain 5%(n=118)	P-value
Base model[*]					
FEA estimated failure load, N	19900 (19544, 20257)	20085 (19809, 20361)	20105 (19921, 20290)	19799 (19326, 20271)	0.54
Integral BMD, mg/cm ³	718.6 (708.2, 729.1)	732.0 (723.9, 740.1)	732.3 (726.9, 737.7)	736.5 (722.7, 750.3)	0.10
Total area, mm ²	444.5 (437.5, 451.6)	439.3 (433.8, 444.7)	438.9 (435.2, 442.5)	431.0 (421.6, 440.4)	0.16
Cortical BMD, mg/cm ³	996.3 (991.6, 1001.0)	998.0 (994.4, 1001.6)	995.3 (992.9, 997.7)	997.1 (990.9, 1003.3)	0.66
Cortical thickness, mm	6.01 (5.89, 6.13)	6.15 (6.06, 6.24)	6.17 (6.11, 6.23)	6.13 (5.98, 6.28)	0.12
Cortical porosity, %	2.26 (2.10, 2.42)	2.11 (1.99, 2.24)	2.11 (2.03, 2.19)	1.87 (1.66, 2.08)	0.04
Multivariable model[†]					
FEA estimated failure load, N	19696(19364, 20029)	19971(19717, 20226)	20175(20004, 20346)	20071(19634, 20507)	0.08
Integral BMD, mg/cm ³	722.0 (711.7, 732.4)	731.9 (724.0, 739.9)	731.6 (726.3, 737.0)	735.0 (721.4, 748.6)	0.36
Total area, mm ²	438.5 (432.2, 444.8)	437.0 (432.2, 441.9)	440.6 (437.4, 443.9)	437.2 (429.0, 445.5)	0.62
Cortical BMD, mg/cm ³	1000.1 (995.6, 1004.6)	998.7 (995.2, 1002.1)	994.3 (992.0, 996.6)	994.6 (988.6, 1000.5)	0.06
Cortical thickness, mm	5.99 (5.87, 6.10)	6.13 (6.04, 6.21)	6.18 (6.12, 6.24)	6.17 (6.02, 6.32)	0.03
Cortical porosity, %	2.23 (2.06, 2.39)	2.12 (1.99, 2.24)	2.12 (2.04, 2.20)	1.88 (1.67, 2.10)	0.09

^{*} adjusted for age, race, and site[†] adjusted for age, race, site, health status, body mass index, limb length and physical activity