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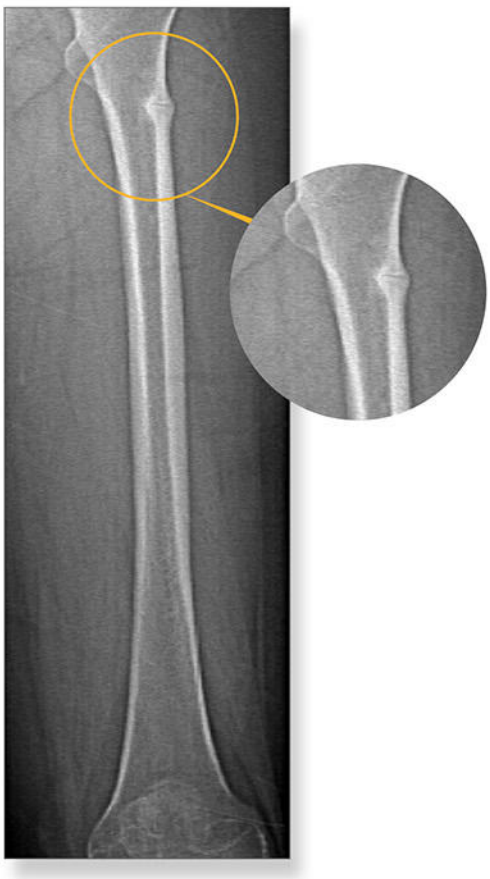

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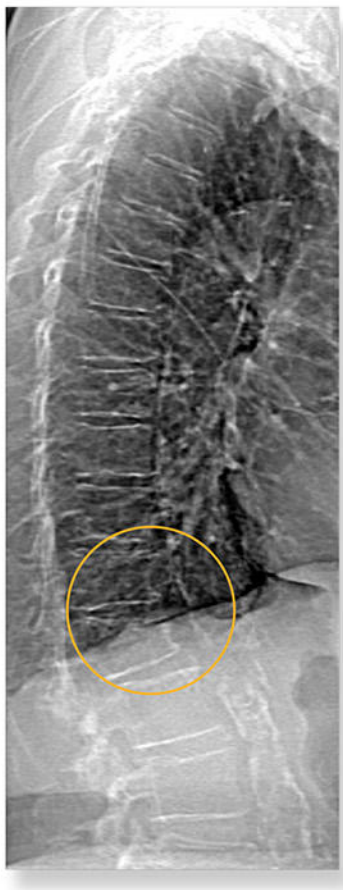

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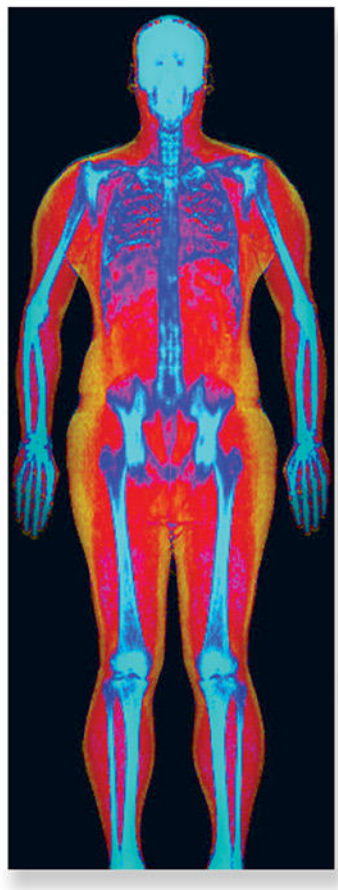

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ORIGINAL ARTICLE

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Long-Term and Recent Weight Change Are Associated With Reduced Peripheral Bone Density, Deficits in Bone Microarchitecture, and Decreased Bone Strength: The Framingham Osteoporosis Study

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ABSTRACT

Weight loss in older adults is associated with increased bone loss and fracture. Little is known about the potential impact of weight loss on cortical and trabecular bone density, microarchitecture, and strength. In this study, participants were members of the Framingham Offspring Cohort (769 women, 595 men; mean age 70 ± 8 years), who underwent high-resolution peripheral quantitative computed tomography (HR-pQCT) scanning at the tibia and radius in 2012 to 2016. Weight measurements taken every 4 to 6 years were used to assess recent weight change over 6 years and long-term change over 40 years. General linear models, adjusting for age, sex, height, smoking, and diabetes, were used to evaluate the association between HR-pQCT indices and relative long-term and recent weight change. We found that long-term and recent weight loss were associated with lower cortical density and thickness, higher cortical porosity, and lower trabecular density and number. Associations were stronger for the tibia than radius. Failure load was lower in those individuals with long-term but not short-term weight loss. Deterioration in both cortical and trabecular indices, especially at the weight-bearing skeleton, characterizes bone fragility associated with long-term and recent weight loss in older adults. © 2018 American Society for Bone and Mineral Research.

KEY WORDS: WEIGHT; WEIGHT LOSS; BONE MICROARCHITECTURE; LONGITUDINAL COHORT STUDY; HR-PQCT

Introduction

Weight loss is associated with bone loss and fracture, and the adverse effect on the skeleton occurs with both unintentional and intentional weight loss.[1] Because weight loss is common in older adults, the clinical implications for skeletal fragility are important. Several mechanisms for weight loss–induced decline in bone mass have been hypothesized, including decreasing mechanical loads on bone due to loss of body mass, lower peripheral conversion of estrogen precursors to estrone resulting from shrinking fat depots, and reduced availability of nutrients owing to changes in diet.[2–4]

Prior observational studies have focused primarily on the association of weight loss with areal bone mineral density (aBMD), assessed by dual-energy X-ray absorptiometry (DXA).[5–12] Although still the gold standard for clinical assessment, two-dimensional DXA images do not measure true volumetric bone density (vBMD), cannot examine cortical and trabecular bone separately, nor do they provide information on bone microarchitecture. Most previous investigations examined recent weight loss, between 2 and 6 years,[6–10] or relied on self-reported rather than measured weight to determine long-term weight loss.[5] Few prospective studies have described how changes in prospectively measured weight over the long term (since early or mid-adulthood) influence bone in late life.[11,12] Thus, understanding of the potential effects of recent versus long-term weight loss on several important determinants of bone strength in older adults is incomplete. The availability of high-resolution peripheral quantitative computed tomography (HR-pQCT) in a cohort

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with many years of repeated measures of body weight allows investigation of the relation between weight loss and several important bone indices, thus helping to elucidate the mechanisms behind weight loss–induced bone loss.

The objective of this study was to determine the association of long-term weight change (over 40 years) and recent weight change (in the past 6 years) with cortical and trabecular vBMD and microarchitecture, and total bone area and strength, assessed by HR-pQCT. We hypothesized that individuals who lost weight, both over the long term and recently, would have lower bone density, deficits in microarchitecture, and reduced bone strength compared with those who did not lose weight, and associations would be most apparent at the weight-bearing tibia versus the non-weight-bearing radius.

Materials and Methods

Study design and participants

Participants for this study included 1361 members (767 women, 594 men) of the Framingham Offspring Cohort. The Framingham Offspring Cohort was established in 1971 with enrollment of 5124 adult children and spouses of members of the original cohort of the Framingham Heart Study, which was enrolled in 1948.[13,14] The original cohort was based on a population-based sample of two-thirds of the residents living in the town of Framingham, MA, USA.[15] Approximately every 4 to 6 years, members of the Offspring Cohort have attended clinic visits with physical examinations, including weight measurements, laboratory tests, and physician-administered interviews.

The current study included participants who attended a clinic visit with HR-pQCT scanning in 2012 to 2016. We considered the clinical visit in 2011 to 2014 as the "index examination." Long-term weight change was calculated from a "baseline" examination (the first clinic visit at enrollment) in 1971 to 1974 to the index examination, and short-term weight change was calculated from a "baseline" examination (the clinic visit preceding the index examination) in 2005 to 2008 to the index examination. Information on covariates was obtained at the index examination. Participants provided written informed consent, and the Institutional Review Boards at Boston University and Hebrew SeniorLife approved the study.

High-resolution peripheral quantitative computed tomography (HR-pQCT)

Volumetric bone density and bone microarchitecture were assessed at the distal tibia and ultradistal radius using HR-pQCT (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland).[16,17] Scans were acquired with a nominal isotropic voxel size of 82 μm^3. The nondominant forearm and right leg were scanned. If a participant reported previous extremity fracture or had metal in the region of the scan, then the contralateral extremity was examined (forearm, $n = 53$ or 5%; tibia, $n = 171$ or 16%). Anteroposterior scout views were used to place a reference line on the distal tibial and radial joint surfaces, as previously described.[18,19] The scan region (110 slices) was 9 mm in length and offset proximally to the reference line by 22.5 mm for the tibia and 9.5 mm for the radius. Scans were evaluated for motion artifacts and repeated if significant movement occurred. Each scan was graded using a 5-point movement artifact scale (1 = none, 2 = minor, 3 = moderate, 4 = severe, and 5 = extreme).[20–22] For density measures, scans with movement artifact-rated grades 1 to 4 were retained, but for microarchitectural measures, only grades 1 to 3 were retained.[16,17] Scanning of a quality-control phantom, containing rods of hydroxyapatite (densities of 0, 100, 200, 400, and 800 mg HA/cm^3), was performed daily to monitor longitudinal stability of the system.

We used the standard analysis program (Scanco software version v6.0) to assess bone cross-sectional area, total density, trabecular density, and trabecular microarchitecture and a semi-automated cortical bone segmentation technique to assess cortical density and cortical microarchitecture.[21,23] We selected as primary bone outcomes trabecular volumetric bone mineral density (Tb.BMD, mgHA/cm^3), trabecular number (Tb.N, 1/mm), trabecular thickness (Tb.Th, mm), cortical volumetric bone mineral density (Ct.BMD, mgHA/cm^3), cortical porosity (Ct.Po, %), cortical thickness (Ct.Th, mm), total (integral) volumetric bone mineral density (Tt.BMD, mgHA/cm^3), and total cross-sectional area (Tt.CSA, mm^2). Micro-finite element analysis (FEA, Numerics88 Solutions Inc., Calgary, Canada) was performed to estimate failure load (N: Newtons), as previously described.[24] Briefly, axial compression conditions were applied with 1% apparent strain and a tissue modulus of 6.829 GPa and Poisson's ratio of 0.3.

Body weight

Weight was measured in pounds using the same protocol at each clinical examination. Participants wearing hospital gowns were weighed to the nearest half pound using a balance beam scale. For the present study, we used weight measurements taken at three time points to calculate long-term weight change and recent weight change: 1) at the index examination in 2011 to 2014; 2) at the previous clinic visit in 2005 to 2008; and 3) at the enrollment clinic visit in 1971 to 1974. Long-term weight change over 40 years was determined between the index examination and enrollment, and recent weight change over 6 years was determined between the index examination and the previous clinic visit.

Covariates

We used information on covariates obtained at the index examination. Information on age, smoking, physical activity (Physical Activity Score for Elderly [PASE]), and prior fracture during adulthood (excluding skull, fingers, toes, and fractures due to trauma) was obtained by physician-administered interviews using standardized questionnaires. Height, to the nearest one-quarter inch, was measured using a stadiometer. Body mass index was calculated as weight (kilograms) divided by the square of height (meters).

Chronic diseases were evaluated by medical history and clinical examination. Diabetes was defined as a fasting plasma glucose level greater than 125 mg/dL (7.0 mmol/dL) or on treatment with insulin or oral hypoglycemic agents. Cardiovascular disease was defined as recognized or unrecognized myocardial infarction (identified by electrocardiogram or enzymes), angina pectoris, or coronary insufficiency. These diagnoses were based on the review of a three-member panel of physicians, who examined all available information including hospital records. Cancer included all cancer sites except nonmalignant skin cancer.

Statistical analysis

We calculated relative long-term weight change (%) by subtracting the weight at enrollment (1971 to 1974) from the

weight at the index examination (2011 and 2014), then dividing by the weight at enrollment. Similarly, we calculated relative recent weight change (%) by subtracting the weight at the previous clinic visit (2005 to 2008) from the weight at the index examination, then dividing by weight at the previous examination. We classified relative long-term and recent weight change into three groups: 1) ≥5% weight loss; 2) <5% weight change; and 3) ≥5% weight gain. Prior studies have used a 5% threshold,[7–9] and these categories allowed sufficient numbers of participants in each group for analysis.

We used linear regression models to estimate beta coefficients for the association between relative weight change, considered in its original form as a continuous variable, and each bone outcome. We performed analysis of covariance (ANCOVA) to estimate least squares means and test for trend in the association between individual bone outcomes and relative weight change groups (≥5% weight loss, <5% weight change, ≥5% weight gain). Initially, we adjusted for age (years), sex, height (inches), current smoking (yes/no), and type 2 diabetes status (yes/no). Subsequently, we further adjusted for physical activity (PASE score) and history of cancer, cardiovascular disease (CVD), and prior fracture (all considered yes/no). Because findings did not differ, we presented results for the parsimonious model.

We performed the following sensitivity analyses. First, we additionally adjusted for baseline weight. Second, we adjusted for covariates assessed at baseline rather than at the index examination. Third, to control for the variability in weight over time in the analyses of long-term weight change, we calculated for each individual the mean and standard deviation of the nine weight measurements from enrollment to the index examination, then additionally adjusted for the standard deviation of this mean. Finally, we performed sex-specific analysis. Statistical analyses were conducted with Statistical Analysis Software SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

The study included 1361 participants, including 767 (56%) women and 594 (44%) men (Table 1). At the index examination, mean age of participants was 70 ± 8 years, and the average weight was 79 ± 17 kg (173 ± 37 lb). Five percent of participants were smokers. Frequencies of a history of diabetes, cancer, CVD, and fracture were 19%, 18%, 8%, and 28%, respectively.

Mean relative long-term weight change was 9% ± 12%, and mean relative recent weight change was –1% ± 6%. Mean values for each weight change group were –9% ± 5%, 1% ± 2%, and 15% ± 10%, respectively, for ≥5% long-term weight loss, <5% long-term weight change, and ≥long-term 5% weight gain, and –8% ± 4%, 0% ± 2%, 7% ± 4%, respectively, for ≥5% recent weight loss, <5% recent weight change, and ≥recent 5% weight gain. Twelve percent of individuals ($n = 166$) had long-term weight loss of 5% or more, whereas 22% ($n = 301$) had recent weight loss of 5% or more (Table 1). Individuals with ≥5% long-term or recent weight loss weighed less, had lower levels of physical activity, and had greater prevalence of diabetes, cancer, CVD, and prior fracture compared with those with ≥5% long-term or recent weight gain.

Unadjusted mean values of tibia and radius cortical density, cortical thickness, trabecular density, trabecular number, total density, and failure load were lower, and cortical porosity was higher, among individuals with long-term or recent weight loss (Table 2). In contrast, unadjusted mean total area appeared to be higher in those with long-term or recent weight loss, whereas unadjusted mean trabecular thickness did not seem lower in the group with long-term or recent weight loss. After adjustment, results largely remained the same (Table 3). However, the strength of association tended to be stronger for the tibia than radius, such that there was a significant trend in all tibia bone indices, but few radius indices, with either or both long-term and recent weight change. Associations with individual bone indices were mostly observed for both long-term and recent weight loss. However, trabecular vBMD and failure load were lower in persons with long-term weight loss but not recent weight loss.

The results of sensitivity analyses were largely similar to the results for our primary analyses. Additional adjustment for baseline weight resulted in similar or somewhat stronger associations (Supplemental Table S1). Adjustment for covariates assessed at baseline rather than at the index examination did not change findings (Supplemental Table S2). Inclusion of the standard deviation of weight measurements over time did not change associations between long-term weight change and bone indices. (Supplemental Table S3). In sex-specific analyses, we found that associations tended to be somewhat stronger in women than men (Supplemental Tables S4 and S5). However, the overall patterns of association were largely consistent with our primary analyses: Stronger trends were observed at the tibia than radius and for long-term than recent weight change.

Discussion

In this large cohort of men and women, those with weight loss had lower peripheral bone density and greater deterioration in microstructure. The strength of association tended to be stronger for the tibia than the radius, and failure load was lower in the tibia and radius only for those individuals with long-term weight loss. Associations were independent of initial weight and variability in weight over time, as well as independent of important confounders.

Our findings are consistent with several previous studies demonstrating that men and women who have recently lost weight, whether intentionally or unintentionally, have lower bone mass[25,26] and experience more bone loss.[7–10,27] These studies have primarily used DXA-derived two-dimensional measures of aBMD at the hip and spine to investigate recent weight loss in the past 2 to 6 years. DXA does not account for bone size and may be affected by changes in the overlying soft tissue.[28]

In contrast to our results, the Tobago Health Study of 1569 men of African descent found weight gain was associated with greater loss of cortical vBMD at the radius and total vBMD at the tibia, assessed by pQCT.[29] The investigators hypothesized that weight gain–related bone micro-damage, increased periosteal bone diameters, suppressed differentiation of mesenchymal stem cells into osteoblasts, decreased physical activity, and poor health status may account for the opposite association they observed between weight change and bone parameters. An alternative explanation may be the relatively younger age of the men in the Tobago Health Study (mean age 57 years), who experienced recent weight gain, whereas the older individuals in our study (mean age 70 years) experienced recent weight loss. Our results also differ from a large cross-sectional study in the MrOS cohort ($n = 3670$ men, mean age 74 years), reporting no association between weight change and trabecular or cortical vBMD at the hip or spine, evaluated by QCT.[25] Weight change

Table 1. Clinical Characteristics of Participants, According to Long-Term and Recent Weight Change

		Long-term weight change[a]			Recent weight change[b]		
	Total	≥5% loss	<5% change	≥5% gain	≥5% loss	<5% change	≥5% gain
	($N = 1361$[c])	($n = 166$)	($n = 275$)	($n = 920$)	($n = 301$)	($n = 834$)	($n = 226$)
Clinical characteristics[d]			Mean ± SD or %			Mean ± SD or %	
Women (*n*)	56	46	46	61	60	53	63
Age (years)	70 ± 8	75 ± 8	71 ± 8	69 ± 7	71 ± 9	70 ± 8	68 ± 7
Height (cm)	163 ± 9	163 ± 10	165 ± 10	163 ± 9	163 ± 10	164 ± 9	163 ± 9
Weight (kg)							
Index examination	79 ± 17	69 ± 14	74 ± 16	82 ± 17	74 ± 16	79 ± 17	82 ± 18
Baseline examination[e]		78 ± 16	73 ± 16	66 ± 14	82 ± 18	79 ± 17	75 ± 17
PASE score	123 ± 65	104 ± 57	120 ± 67	127 ± 65	116 ± 67	124 ± 65	125 ± 63
Current smoker	5	5	5	5	5	4	9
Diabetes	19	22	24	17	26	18	15
Cancer	18	19	18	18	17	19	15
CVD	8	12	8	7	9	7	9
Prior fracture	28	31	33	26	29	29	26

PASE = Physical Activity Scale for Elderly; CVD = cardiovascular disease.

[a]Long-term (40-year) weight change was determined between the index examination (2011–2014) and enrollment (1971–1974) and expressed as a percentage of the weight at the index examination.

[b]Recent (6-year) weight change was determined between the index examination and the preceding clinic visit (2005–2008) and expressed as a percentage of the weight at the preceding clinic visit.

[c]The sample includes 1361 individuals with HR-pQCT measures at the tibia ($n = 1328$) and/or radius ($n = 1263$).

[d]Clinical characteristics were assessed at index examination (2011–2014) unless otherwise noted.

[e]The baseline examination was at enrollment (1971–1974) for long-term weight change and at the preceding clinic visit (2005–2008) for recent weight change.

was determined from participant recall of weight at age 25 years, in contrast to weight measured over 40 years in our study. However, a longitudinal analysis of measured weight change over 1.8 years in the same MrOS cohort found men who experienced weight loss had higher rates of bone loss at the hip, assessed by DXA.[30] Thus, although results from some studies may differ from ours, the discordance is most likely attributable, at least in part, to differences in demographic characteristics of participants and variations in the methods to evaluate weight change and bone outcomes.

Our findings showing that individuals who experience long-term weight loss have lower peripheral bone density and alterations in microstructure are consistent with the limited number of investigations based on repeated weight measurements over long durations of time. In a large study of Norwegian middle-aged men ($n = 1476$), Meyers and colleagues[11] found an inverse association between weight loss over 30 years and hip aBMD, assessed by DXA. In a 15-year longitudinal study of women in the Chingford Study ($n = 995$), Zhai and colleagues[12] reported increased bone loss at the hip and spine aBMD, assessed by DXA. Our study confirms and extends prior work by showing that long-term weight loss, independent of chronic diseases and other risk factors, adversely affects both cortical and trabecular bone microarchitecture and density, especially at the weight-bearing skeleton, in women and men.

There are several mechanisms that might explain why weight loss leads to lower bone density and deteriorated microarchitecture. Possibilities include reduced skeletal loading, a changing hormonal milieu, and nutritional changes such as reduced protein intake. Our findings that tibial measures were more consistently associated with weight loss when compared with radial measures support the mechanism of reduced skeletal loading. A case-control study of 25 women (aged 18 to 40 years) with anorexia nervosa and 25 female controls matched on age and height found that deficits in cortical thickness and estimated failure load were more pronounced in the weight-bearing tibia compared with the non-weight-bearing radius, implying a direct effect of low body weight on bone loss in anorexia nervosa.[31] Our observation of worse bone outcomes at the tibia than the radius after weight loss is consistent with these findings in anorexic individuals.

As might be expected, there were fewer individuals who lost 5% or more weight in the past 40 years (12%) than over the past 6 years (22%). Despite this difference, we nevertheless observed the same pattern of associations with bone density and microarchitecture for both long-term and recent weight loss. An interesting finding, however, was that the lower values for many of the microarchitecture measures that were observed in the weight loss group were accompanied by an increase in the total area of the bone. This suggests the possibility that as loading of the skeleton is reduced with weight loss, the reduction in bone density and cortical thickness may lead to a compensatory expansion of the periosteal surface to maintain bone strength. It is noteworthy that the magnitude of the difference in total area between the recent weight loss and recent weight gain groups was not as pronounced as that observed over longer periods. This further supports our hypothesis that periosteal expansion may take a while to occur in the face of decreasing bone density. Another possibility is that individuals who lost weight were heavier during the time of skeletal growth when bone area was being established. Ultimately, despite the possibility of compensatory changes in bone area, bone strength decreases with weight loss, as shown by the lower failure loads in the weight loss group. Nevertheless, it is possible that these lower failure loads may be "appropriate" for the reduced body weight. Prospective studies of weight

Table 2. Unadjusted Means (± SD) for HR-pQCT Indices at the Tibia and Radius, According to Long-Term and Recent Weight Change Group

		Weight change[a]					
		Long term			Recent		
	Total	≥5% loss	<5% change	≥5% gain	≥5% loss	<5% change	≥5% gain
HR-pQCT indices				Mean ± SD or %[b]			
Tibia	$n = 1328$[c]	$n = 163$	$n = 269$	$n = 896$	$n = 299$	$n = 810$	$n = 219$
Ct.BMD (mgHA/cm^3)	851.8 ± 79.7	821.1 ± 87.4	839.4 ± 84.7	861.1 ± 74.8	835.6 ± 86.9	854.8 ± 77.1	862.6 ± 76.2
Ct.Po (%)	10.173 ± 3.446	11.069 ± 3.805	10.779 ± 3.497	9.832 ± 3.310	10.736 ± 3.840	10.139 ± 3.346	9.520 ± 3.111
Ct.Th (mm)	1.188 ± 0.308	1.097 ± 0.343	1.173 ± 0.341	1.209 ± 0.288	1.150 ± 0.325	1.197 ± 0.299	1.207 ± 0.316
Tb.BMD (mgHA/cm^3)	176.3 ± 41.0	173.3 ± 46.1	179.9 ± 42.8	175.7 ± 39.4	174.7 ± 43.2	177.7 ± 40.3	173.1 ± 40.3
Tb.N (1/mm)	2.065 ± 0.403	2.008 ± 0.439	2.072 ± 0.409	2.073 ± 0.394	2.022 ± 0.434	2.080 ± 0.392	2.065 ± 0.396
Tb.Th (mm)	0.072 ± 0.012	0.072 ± 0.013	0.073 ± 0.013	0.071 ± 0.012	0.072 ± 0.012	0.072 ± 0.012	0.070 ± 0.013
Tt.Ar (mm^2)	773.5 ± 164.9	817.1 ± 173.2	800.7 ± 173.2	757.5 ± 158.4	770.5 ± 173.7	782.8 ± 164.9	743.5 ± 148.7
Tt.BMD (mgHA/cm^3)	284.3 ± 61.1	265.4 ± 68.3	282.7 ± 62.8	288.2 ± 58.5	276.8 ± 66.0	286.2 ± 59.4	287.3 ± 59.7
FL (N)	6443 ± 1767	6301 ± 1941	6662 ± 1941	6404 ± 1674	6237 ± 1880	6569 ± 1758	6258 ± 1591
Radius	$n = 1263$[c]	$n = 143$	$n = 252$	$n = 868$	$n = 278$	$n = 774$	$n = 211$
Ct.BMD (mgHA/cm^3)	947.2 ± 69.8	928.1 ± 71.8	941.9 ± 65.1	951.9 ± 70.3	940.9 ± 73.5	947.5 ± 67.0	954.3 ± 74.5
Ct.Po (%)	3.942 ± 1.727	4.300 ± 1.715	4.200 ± 1.678	3.812 ± 1.728	3.972 ± 1.732	3.992 ± 1.683	3.724 ± 1.861
Ct.Th (mm)	0.864 ± 0.221	0.818 ± 0.234	0.860 ± 0.234	0.873 ± 0.214	0.830 ± 0.226	0.872 ± 0.215	0.880 ± 0.230
Tb.BMD (mgHA/cm^3)	164.4 ± 42.9	161.5 ± 46.2	165.5 ± 45.9	164.5 ± 41.4	161.1 ± 44.1	165.1 ± 41.9	165.8 ± 44.6
Tb.N (1/mm)	2.053 ± 0.373	1.998 ± 0.390	2.026 ± 0.398	2.070 ± 0.361	2.010 ± 0.416	2.071 ± 0.362	2.046 ± 0.347
Tb.Th (mm)	0.067 ± 0.011	0.068 ± 0.012	0.068 ± 0.012	0.066 ± 0.011	0.067 ± 0.012	0.067 ± 0.011	0.067 ± 0.012
Tt.Ar (mm^2)	306.3 ± 80.6	320.6 ± 76.8	323.6 ± 82.8	298.9 ± 79.5	304.7 ± 85.0	310.1 ± 79.8	294.2 ± 76.5
Tt.BMD (mgHA/cm^3)	311.2 ± 68.6	294.8 ± 71.5	306.9 ± 67.1	315.1 ± 68.1	302.8 ± 69.9	312.2 ± 66.7	318.5 ± 72.8
FL (N)	2530 ± 795	2529 ± 814	2646 ± 868	2497 ± 768	2454 ± 801	2570 ± 798	2486 ± 771

Ct.BMD = cortical volumetric bone mineral density; Ct.Po = cortical porosity; Ct.Th = cortical thickness; Tb.BMD = trabecular volumetric bone mineral density; Tb.N = trabecular number; Tt.BMD = total (integral) volumetric bone mineral density; Tt.CSA = total cross-sectional area; FEA = micro-finite element analysis; FL = failure load.

[a]Long-term (40-year) weight change was determined between the index examination (2011–2014) and enrollment (1971–1974) and expressed as a percentage of the weight at the index examination. Recent (6-year) weight change was determined between the index examination and the preceding clinic visit (2005–2008) and expressed as a percentage of the weight at the preceding clinic visit.

[b]Unadjusted.

[c]The sample includes 1361 individuals with HR-pQCT measures at the tibia ($n = 1328$) and/or radius ($n = 1263$).

change and incident fracture are needed to fully evaluate these hypotheses.

Even though the patterns of associations with HR-pQCT indices were largely consistent across long-term weight change versus short-term weight change, failure load was lower in persons with long-term weight loss, but not in persons with recent weight loss, suggesting that skeletal fragility may not occur with weight loss over the short term but will occur over a longer period.

To determine the clinical significance of our findings, we estimated the risk of fracture associated with the magnitude of the observed differences in HR-pQCT indices according to long-term weight change. Thus we applied the hazard ratio (HR) for the association between incident fracture and tibia trabecular vBMD reported for postmenopausal women in the Calgary CaMos Cohort: HR = 1.7, per SD decrease.[32] We observed a difference of 1.6 standard deviations in mean tibia trabecular vBMD between women with 5% or more long-term weight loss (150.7 ± 5.4 mgHA/cm^3) and those with stable weight (158.3 ± 4.5 mgHA/cm^3). Thus, we estimated that women who lose 5% or more weight over 40 years may have a 2.7 times increase in the incidence of fracture. In other words, the magnitude of association between weight loss and HR-pQCT indices in the peripheral skeleton may have an important clinical impact on fracture risk in older adults.

This study has several strengths. We used state-of-the-art HR-pQCT imaging to measure volumetric bone density and microarchitecture in the cortical and trabecular compartments and applied micro-finite element analyses to provide an integrated assessment of bone strength. However, with only a single HR-pQCT assessment, we are unable to evaluate the influence of weight change on longitudinal changes in bone structure over time. In addition, the resolution of the first-generation HR-pQCT scanner precludes direct analysis of trabecular thickness. Rather, trabecular thickness is derived from trabecular density and trabecular number, assuming a platelike structure. Further, the threshold-based approach for detection of cortical porosity likely underestimated cortical porosity. This could lead to nondifferential bias resulting in underestimation of the study findings.

Our use of repeatedly measured weight, obtained over four decades preceding the bone measures, is an important strength of this study. Prior work that relied on recall of prior recent weight[5,25,26] can be subject to bias, and few studies measured long-term weight change.[11,12] However, our study did not have information available as to whether weight change was voluntary or involuntary.[9] Thus, we cannot be certain that the weight change itself was responsible for the differences in bone measures or factors related to the weight change. Importantly, our results were independent of diabetes, cancer, cardiovascular disease, and prior fracture, as well as several other potential confounders that are well characterized in the Framingham Study. Nevertheless, it is possible that our results may have been affected by residual confounding, as in all observational studies.

Table 3. Association Between Long-Term and Recent Weight Change and HR-pQCT Indices at the Tibia and Radius, Adjusted for Age, Sex, Height, Current Smoking, and Diabetes (Beta Coefficients Are Presented for Weight Change Treated as a Continuous Variable, and Least Square Means Are Presented for Weight Change Group)

	Weight change[a]											
	Long term						Recent					
	Continuous		Categorical measure				Continuous		Categorical measure			
	β	*p* Value[b]	≥5% loss ($n = 166$)[a]	<5% change ($n = 275$)[a]	≥5% gain ($n = 920$)[a]	*p* Value [b]	β	*p* Value[b]	≥5% loss ($n = 301$)[a]	<5% change ($n = 834$)[a]	≥5% gain ($n = 226$)[a]	*p* Value[b]
HR-pQCT indices												
Tibia ($n = 1328$)[c]				Mean[d]						Mean[d]		
Ct.BMD (mgHA/cm^3)	0.6916	<**0.0001**	833.3	839.1	858.2	<**0.0001**	1.0274	**0.0001**	838.9	853.0	857.2	**0.0031**
Ct.Po (%)	−0.0163	**0.0020**	10.567	10.749	10.082	0.0934	−0.0405	**0.0014**	10.718	10.256	9.904	**0.0057**
Ct.Th (mm)	0.0027	<**0.0001**	1.125	1.169	1.228	<**0.0001**	0.0028	**0.0033**	1.175	1.202	1.222	**0.0347**
Tb.BMD (mgHA/cm^3)	0.1683	**0.0045**	168.0	173.8	174.8	**0.0363**	−0.0009	0.9949	172.9	173.9	173.4	0.8765
Tb.N (1/mm)	0.0040	<**00001**	1.973	2.023	2.087	**0.0003**	0.0037	**0.0069**	2.021	2.059	2.093	**0.0252**
Tb.Th (mm)	−0.0001	**0.0066**	0.072	0.072	0.070	0.2709	−0.0001	**0.0251**	0.072	0.071	0.070	**0.0467**
Tt.Ar (mm^2)	−0.3338	**0.0334**	800.2	780.3	769.2	**0.0003**	−0.6510	0.0833	782.9	777.9	763.8	**0.0295**
Tt.BMD (mgHA/cm^3)	0.5612	<**0.0001**	266.3	278.1	288.1	<**0.0001**	0.4994	**0.0131**	277.2	283.5	287.1	**0.0344**
FL (N)	6.9252	<**0.0001**	6251	6402	6492	**0.0074**	5.4482	0.1659	6372	6478	6413	0.6548
Radius ($n = 1263$)[c]												
Ct.BMD (mgHA/cm^3)	0.2526	**0.0175**	941.0	943.8	946.1	0.4019	0.4658	0.0701	941.1	946.1	946.1	0.4065
Ct.Po (%)	−0.0029	0.2854	4.013	4.140	3.992	0.8977	−0.0036	0.5919	4.040	4.050	3.961	0.6099
Ct.Th (mm)	0.0015	<**0.0001**	0.836	0.853	0.881	**0.0109**	0.0023	**0.0024**	0.844	0.873	0.885	**0.0208**
Tb.BMD (mgHA/cm^3)	0.2546	<**0.0001**	158.2	160.7	166.2	**0.0240**	0.2740	0.0664	161.6	163.3	167.5	0.0888
Tb.N (1/mm)	0.0033	<**0.0001**	1.983	2.010	2.107	**0.0002**	0.0028	**0.0420**	2.030	2.080	2.081	0.1150
Tb.Th (mm)	0.0000	0.5956	0.066	0.066	0.066	0.5388	0.0000	0.9516	0.066	0.065	0.066	0.8347
Tt.Ar (mm^2)	−0.0995	0.1914	313.6	315.1	312.0	0.7115	−0.1151	0.5320	315.6	313.1	309.2	0.1374
Tt.BMD (mgHA/cm^3)	0.5562	<**0.0001**	298.8	304.1	314.9	**0.0057**	0.6592	**0.0078**	303.5	310.5	317.0	**0.0189**
FL (N)	1.9216	**0.0125**	2478	2549	2567	**0.0447**	2.5247	0.1748	2519	2560	2564	0.2887

Ct.BMD = cortical volumetric bone mineral density; Ct.Po = cortical porosity; Ct.Th = cortical thickness; Tb.BMD = trabecular volumetric bone mineral density; Tb.N = trabecular number; Tt.BMD = total (integral) volumetric bone mineral density; Tt.CSA = total cross-sectional area; FEA = micro-finite element analysis; FL = failure load.

[a]Long-term (40-year) weight change was determined between the index examination (2011–2014) and enrollment (1971–1974) and expressed as a percentage of the weight at the index examination. Recent (6-year) weight change was determined between the index examination and the preceding clinic visit (2005–2008) and expressed as a percentage of the weight at the preceding clinic visit.

[b]Bold indicates *p* values < 0.05.

[c]The sample includes 1361 individuals with HR-pQCT measures at the tibia ($n = 1328$) and/or radius ($n = 1263$).

[d]Adjusted for age, sex, height, current smoking, and diabetes.

Our study included a large, community-based population of women and men. However, participants are predominantly white, so our findings may not be fully generalizable to other race and ethnic groups. In addition, our study included a "survivor cohort," that is, members of the Framingham Study who survived 40 years from study entry (1971 to 1974) until the time of bone measurements (2012 to 2016). Cohort members who did not survive were more likely to have had poor health status, including (unintentional) weight loss and skeletal fragility, than the individuals included in this study. As a result, we may have underestimated the association between weight loss and skeletal deficits. We had fewer men than women, which may have reduced our power to detect associations in sex-specific analyses, particularly in men.

Our findings showing stronger associations at the weight-bearing tibia than the non-weight-bearing radius support a role for weight loss–induced decreased loading in skeletal fragility. Alternatively, radial scans are more prone to movement artifact and lower precision than tibia scans. As a result, measurement error may have been greater at the radius, thereby potentially reducing the ability to detect associations at this site.

In conclusion, our results suggest both recent and long-term weight loss may adversely affect cortical and trabecular bone density and microarchitecture at the weight-bearing skeleton. Given that weight loss is highly common in older adults, further work is needed to evaluate if these deficits can be prevented through interventions or therapy.

Disclosures

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Authors' roles: CTL, MLB, DPK and EJS conceived the concept of the work and planed the study design and analysis. CTL and HX conduct the statistical analysis. CTL, SS, HX, RRM, DPK and EJS drafted the manuscript. All authors discussed the results as well as reviewed and approved the final manuscript.

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