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Evaluating the relationship between muscle and bone modeling response in older adults

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Abstract

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Appendix A. Supplementary data: Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.bone.2016.06.012>.

Bone modeling, the process that continually adjusts bone strength in response to prevalent muscle-loading forces throughout an individual's lifespan, may play an important role in bone fragility with age. Femoral stress, an index of bone modeling response, can be estimated using measurements of DXA derived bone geometry and loading information incorporated into an engineering model. Assuming that individuals have adapted to habitual muscle loading forces, greater stresses indicate a diminished response and a weaker bone. The purpose of this paper was to evaluate the associations of lean mass and muscle strength with the femoral stress measure generated from the engineering model and to examine the extent to which lean mass and muscle strength account for variation in femoral stress among 2539 healthy older adults participating in the Health ABC study using linear regression. Mean femoral stress was higher in women (9.51, SD = 1.85 Mpa) than in men (8.02, SD = 1.43 Mpa). Percent lean mass explained more of the variation in femoral stress than did knee strength adjusted for body size ($R^2 = 0.187$ vs. 0.055 in men; $R^2 = 0.237$ vs. 0.095 in women). In models adjusted for potential confounders, for every percent increase in lean mass, mean femoral stress was 0.121 Mpa lower (95% CI: — 0.138, — 0.104; $p < 0.001$) in men and 0.139 Mpa lower (95% CI: — 0.158, — 0.121; $p < 0.001$) in women. The inverse association of femoral stress with lean mass and with knee strength did not differ by category of BMI. Results from this study provide insight into bone modeling differences as measured by femoral stress among older men and women and indicate that lean mass may capture elements of bone's response to load.

Keywords

Femoral stress; Bone modeling response; Muscle

1. Introduction

Bone fragility in older adults leads to fracture, resulting in high health care costs, poor health outcomes, disability and death [1]. Most investigations of bone fragility have focused on the apparent remodeling imbalance between bone formation and resorption that reduces bone mineral density (BMD) with age [2–5]. However, anomalies in bone modeling may also play a critical role in the skeletal fragility of aging. Modeling is the process that continually adjusts skeletal strength to resist prevalent forces (loads) or described in terms of the Frost Mechanostat, where bone tissue is added or removed to ensure that minute deformations (strains) of bone tissue remain within some ‘normal’ range [6–8]. Bones may become weak because they either adapted to reduced loads or because they have a diminished response to load. Individuals with a normal response to reduced load as a result of disuse (e.g. becoming sedentary) will have strains that remain below the upper threshold for adaptation and will have weaker bones in absolute terms. Individuals with a diminished response to load (i.e.: abnormal bone modeling) will require higher strains to cause bone formation. In other words, the upper threshold has increased which means less bone tissue and higher strains relative to typical loading forces. Measuring bone's modeling response may better capture aspects of bone homeostasis that determine bone strength relative to a simple measure like areal BMD.

The forces that stimulate bone modeling are thought to be muscle load induced strains, or minute deformations of loaded tissue detected by osteocytes distributed within the lacunar spaces [9]. Assuming that the skeleton is fully adapted to prevalent loading forces, the strains generated by those loads should be an index of bone modeling response. We expect that individuals with a deficient response have less bone mass relative to the forces the bone typically experiences, which will result in higher than average strains and more fragile bone.

Currently, skeletal tissue strains cannot be measured non-invasively. Fortunately, stresses, which are proportional to strain, quantify the concentration of loading force at a specific location on the bone and can be computed using measurements of bone geometry with loading information incorporated into an engineering model. In this paper we use an engineering model to compute stress generated at the medial cortex of the femoral neck in a one-legged stance. Stress is concentrated at this site under stance loads and the bone tissue properties remain unchanged in older age [10]. Stress ('force concentration') is a function of bone geometry (dimensions) and the direction and magnitudes of loading forces assuming that bone material properties are constant. Our model employed Dual Energy X-ray Absorptiometry (DXA) derived hip geometry combined with information about forces at the hip under a single body weight force [11,12]. We know from biomechanical studies that hip forces are a multiplicative function of body weight that increases with the type and intensity of physical activity that the individual normally experiences. Unless we use the right force (or correct for it) in our current model, we cannot tell whether higher stresses are due to reduced muscle load or a deficiency in response to load. To differentiate the reasons for a high stress measure, we would either need an invasive way to confirm deficiencies in cellular response to load or a direct measure of muscle forces to see if an individual has higher stress than expected given the level of force. As a result, the best we can do is account for measures of muscle load in our assessment of femoral stress.

The purpose of this paper is to evaluate the associations of lean mass and muscle strength with the femoral stress measure generated from the engineering model and to examine the extent to which lean mass and muscle strength account for variation in femoral stress among a cohort of healthy older adults. The remaining heterogeneity after accounting for indicators of muscle load may be an index of modeling response. Results from this study will provide context for future studies of bone modeling response and provide a method for evaluating the important role that muscle plays in this relationship.

2. Methods

2.1. Study population

The Health Aging and Body Composition (Health ABC) study cohort includes 1491 men (37% black) and 1584 women (46% black) aged 70–79 at time of enrollment. Participants were recruited using Medicare beneficiary listings from Pittsburgh, Pennsylvania and Memphis Tennessee between May 1997 and July 1998. Eligibility criteria included no self-reported difficulty with walking one quarter mile or climbing 10 stairs without resting; no difficulty performing activities of daily living; and no reported use of an ambulatory aid including a cane, walker, crutches or other special equipment. Eligibility criteria also

included no history of active treatment for cancer in the prior 3 years, no enrollment in a lifestyle intervention trial and no plan to move out of the area in the following 3 years [13].

The analytic sample for this cross-sectional analysis included 1252 men and 1287 women who had a DXA scan analyzed using the Hip Structural Analysis (HSA) program and all measured covariates described below (Fig. 1). Compared to the analytic sample, the 526 men and women without all measured covariates were significantly older and reported more co-morbidity and poorer health, and took more medications. Compared to the analytic sample, men without all measured covariates were significantly shorter and more likely to be black.

2.2. Femoral stress estimation

Bone geometry was measured using the Hip Structural Analysis program from dual energy x-ray absorptiometry data [14]. The HSA software generates geometry from profiles of pixel values traversing the proximal femur at its narrowest point when viewed in a frontal plane DXA image. The software also provides information to locate the center of the femoral head in order to estimate the weight vector, the neck-shaft angle, the vector distances to the femoral neck cross-section, the abductor force and the ground reaction force vectors. Femoral stress was estimated on the medial aspect of the neck cross-section using a body weight load as follows:

$$\sigma = \frac{My}{I} + \frac{F}{A}$$
 where M represents the net bending moment orthogonal to the neck axis, I is the HSA-derived cross sectional moment of inertia (CSMI) for bending in the frontal plane; A represents the bone surface in the cross section (CSA); y represents the displacement of the medial surface from the neutral axis and F represents axial component of loading force. Forces were computed at the medial cortex of the femoral neck in a one legged stance using body weight (in Newtons) and femur length estimated from height using forensic formulas [15]. Using the formalism employed by McLeish et al., the gravitational load on the femoral head (joint force) is assumed to be 5/6 body weight, the ground reaction forces at the knee is 8/9 of body weight and the abductor force is oriented at an angle of 19 degrees to the horizontal with the magnitude computed to achieve static equilibrium [16]. Forces in the frontal plane are represented in the left diagram in Fig. 2, and are resolved to their x and y components in the right (i.e., F_{Mx} , F_{My} , F_{Jx} , F_{Jy}). Forces are then balanced to ensure that all components in the x and y directions sum to zero.

2.3. Muscle loading forces

2.3.1. Knee muscle strength—Isokinetic knee extension strength was measured using a KinCom 125 AP dynamometer (Cattanooga, TN) at 60° per second. The average torque (measured in Newton meters) from three reproducible trials was used. Participants with a medical condition including a systolic blood pressure ≥ 200 mmHG, diastolic blood pressure ≥ 110 mmHG or who reported a history of cerebral aneurysm, cerebral bleeding, bilateral total knee replacement, or severe bilateral knee pain were excluded from testing [13,17].

2.3.2. Muscle Mass—Bone Free Total body lean mass was measured from whole body DXA scans conducted on Hologic 4500A machines at both study centers (Hologic, Waltham, MA). [17].

2.4. Covariates

Age, race, number of co-morbidities, general health status, number of medications, alcohol use, smoking, and walking ability were included in final analyses. Age was recorded in years and participants' race was categorized as either white or black. Number of co-morbidities was measured via self-report of the following conditions: osteoarthritis, coronary heart disease including a history of angina, myocardial infarction, congestive heart failure, stroke, diabetes, and chronic obstructive pulmonary disease. Health status was measured using self-rated health and categorized as excellent/very good, good, or fair/poor. Medication use was assessed at the time of the first clinic visit and was treated as a continuous variable (number of medications taken). Alcohol use was reported as the number of drinks consumed per week over the last year and was categorized into three groups: 1–3 drinks, 4–6 drinks and 7 or more drinks per week. To assess smoking, people were categorized based on having ever smoked 100 cigarettes or not. Walking ability was based on the ease with walking a quarter mile and 1 mile and is used in this analysis as a measure of function. People who found walking this distance “very easy” were compared to all others. Regression analysis also controlled for study site.

2.5. Statistical analysis

Differences in participant characteristics were compared across quartiles of femoral stress separately for men and women using a non-parametric test for trend across ordered groups. To account for the confounding effects of body size on lean mass and knee strength, total body lean mass was divided by total body mass to compute percent lean mass; and isokinetic knee torque was divided by total body mass to compute a measure of knee strength adjusted for body mass. To quantify the strength of linear relationship, we computed partial correlations of femoral stress with percent lean mass and body mass adjusted isokinetic knee strength adjusted for study site. Linear regression was used to model the association of femoral stress with percent lean mass and body mass adjusted isokinetic knee strength. Four sets of sex-stratified models were generated. The first set of models included percent lean mass and study site (model 1). The second set of models included body mass adjusted isokinetic knee strength and site (model 2). The third set of models included both percent lean mass and body mass adjusted isokinetic knee strength, and site (model 3). The fourth set of models included both percent lean mass, body mass adjusted isokinetic knee strength, site and all covariates described above (model 4). We did not include total body mass in our models because both the measures of femoral stress and the measures of lean mass and muscle strength are normalized to total body mass. In this analysis, we aim to determine whether the composition of mass (lean vs. non-lean) affects stress. As a sensitivity analysis, we also ran these analyses stratified by BMI to see whether results differed by category of body size. Additional sensitivity analyses were conducted to determine whether linear regression results differed when using other methods to classify lean mass (e.g. appendicular lean mass/BMI). We also refit the models excluding outliers to address their impact on the

results. All analyses were conducted using STATA statistical software version 9 (Stata, College Station, TX, USA).

3. Results

3.1. Descriptive characteristics

Demographic information, health status, function, body composition and bone geometry for men and women are described in Table 1 by quartile of femoral stress. Mean femoral stress was higher in women (9.51; SD = 1.85 MPas) than in men (8.02; SD = 1.43 MPa), where higher stress indicates weaker bones. For the purposes of illustration, mean BMD, CSA and CSMI at the femoral neck are also shown by stress quartile. Note that CSA and CSMI, which are used in the calculations of stress, are expectedly lower in higher quartiles of femoral stress, with an analogous inverse pattern for BMD and femoral stress (Table 1).

Femoral stress was not significantly associated with age, race, health status or medication use in men; but in women. Whites had lower femoral stress compared with Blacks ($p < 0.001$). In both men and women, fewer people with high (compared with low) femoral stress found it very easy to walk at least a quarter mile ($p < 0.03$) (Table 1).

3.2. Relationship of femoral stress with body size and muscle loading forces

Weight was positively associated with femoral stress, owing to the use of weight to approximate the forces in measuring femoral stress. In both men and women, average weight increased across quartiles of femoral stress. However, individuals with a higher proportion of lean mass relative to their total mass had lower femoral stress. Average percent lean mass was 65% (SD = 4.1) in men in the highest quartile of femoral stress compared with 70% (SD = 4.7) in men in the lowest quartile ($p < 0.001$). Similarly, the average percent lean mass was 53.5% (SD = 4.4) in women in the highest quartile of femoral stress compared with 60% (SD = 5.7) in women in the lowest quartile ($p < 0.001$). Likewise, men and women with higher knee strength relative to their total body mass had significantly lower femoral stress.

Partial correlations (adjusted for study site) of femoral stress with percent total body lean mass were -0.40 in men and -0.45 in women; the correlations of femoral stress with body mass adjusted isokinetic knee strength n were -0.16 in men and -0.24 in women, indicating that femoral stress is more strongly linearly associated with lean mass than with knee strength. In both men and women, the correlation between femoral stress and percent lean mass was stronger than the correlation between body mass adjusted isokinetic knee strength. Table 2 provides coefficients from linear regression models of femoral stress on percent lean mass and body mass adjusted isokinetic knee strength. In men, results from model 1 showed that for every percent increase in lean mass, mean femoral stress was 0.122 MPa lower (95% CI: -0.138 , -0.107 ; $p < 0.001$) and model 2 showed that for every unit increase in body mass adjusted isokinetic knee strength, mean femoral stress was 0.62 MPa lower (95% CI: -0.833 , -0.403 ; $p < 0.001$). Percent lean mass explained more of the variability in femoral stress ($R^2 = 0.1867$) than isokinetic knee strength ($R^2 = 0.0547$). Results from model 3 showed that when both percent lean mass and body mass adjusted isokinetic knee strength were included in the regression model, only percent lean mass was

significantly associated with femoral stress. The relationship between percent lean mass and femoral stress did not change after including other covariates in model 4. In women, results from model 1 showed that for every percent increase in lean mass, mean femoral stress was 0.152 MPa lower (95% CI: — 0.168, — 0.135; $p < 0.001$) and model 2 showed that for every unit increase in body mass adjusted isokinetic knee strength, mean femoral stress was 1.49 MPa lower (95% CI: — 1.82, — 1.16; $p < 0.001$). As in men, percent lean mass explained more of the variability in femoral stress ($R^2 = 0.2374$) than isokinetic knee strength ($R^2 = 0.0946$). Results from model 3 showed that when both percent lean mass and body mass adjusted isokinetic knee strength were included in the regression model, both were significantly associated with femoral stress, but the strength of the association between isokinetic knee strength and femoral stress was substantially diminished ($B = -0.339$ 95% CI: — 0.067, — 0.001 vs, — 1.49 95% CI: — 1.82, — 1.16) after accounting for lean mass. Results did not change substantially after including other covariates in model 4, though knee strength was no longer significantly associated with femoral stress. Other methods to classify lean mass (e.g. ALM/BMI) provided similar results (data not shown). Results from models that were fit excluding three outliers were qualitatively unchanged.

3.3. Relationship of femoral stress with body size and muscle loading forces stratified by BMI

Results were also similar when stratified by category of BMI. However in fully adjusted models, knee strength was positively associated with femoral stress in obese men and in underweight, normal weight and obese women, although these associations were not statistically significant (Tables 3 and 4).

4. Discussion

The purpose of this paper was to evaluate the relations of muscle mass and muscle strength with a measure of bone modeling response (femoral stress) among older men and women. Differences in femoral stress may indicate variations in adaptation to load that lead to weaker, more fracture-susceptible bones. To effectively compare individuals, we need to account for variability in modeling response that come from differences in muscle loading forces. Current methods for estimating femoral stress do not directly incorporate information about these forces. Here, we accounted for muscle load by evaluating the relative independent contributions of both lean mass and muscle strength to femoral stress.

Our data show stronger correlations between percent lean mass and femoral stress (compared with knee strength and femoral stress), consistent with results from a recent study that examined the cross sectional relationship between muscle mass, muscle strength and bone strength parameters among older men and women [18]. Results from that study showed that correlations between muscle mass and bone strength were twofold higher than the correlations between knee strength and bone strength parameters. We found that in both men and women, controlling for percent lean mass accounted for more variability in femoral stress than controlling for body mass adjusted isokinetic knee strength, as measured by the R^2 . In women, percent lean mass and body mass adjusted isokinetic knee strength were significantly associated with femoral stress independent of each other after adjusting for

potential confounders. In men, however, only percent lean mass was significantly associated with femoral stress in fully adjusted models. Results were similar in sensitivity analyses when using other methods to classify lean mass such as ALM/BMI; a measure commonly used in studies of sarcopenia among older adults [19].

Nevertheless, in both men and women, 75–80% of the variation in femoral stress remains unexplained even after accounting for indicators of muscle load and a range of demographic and health variables. The remaining variability likely reflects individual variation in bone modeling response to load. Although the focus of this study was on muscle effects, hormonal and genetic factors also play an important role in the regulation of this physiologic process and may explain differences in femoral stress among individuals as well as differences in femoral stress that we observed in this study between men and women [7]. These differences may be due to gender-specific hormonal interactions with muscle tissue that result in changes to muscle mass and strength thereby affecting the load on bone [20]. For example, it is likely that postmenopausal estrogen deficiency contributes to alterations in the modeling response resulting in weaker bones and higher stresses in older women compared to older men [7,21]. Fat mass may also play a role in bone adaptation to load, and it's possible we may be inadvertently detecting an association with fat mass in our analyses. However results did not differ in men or women when stratified by categories of BMI suggesting our estimate of lean mass likely reflects the effects of muscle we aimed to evaluate.

This study has several strengths. First, it is novel in the sense that while the relationship between muscle mass, muscle strength and bone is well established in children and adolescents [22], these relationships have not been well defined in older adults. The Health ABC study is unique in its collection of extensive indicators of body composition in a well-characterized community-dwelling population of older adults providing an ideal data source for exploring the relationships between muscle and bone. Second, previous studies in adults have employed models using three dimensional data and finite element modeling techniques to measure bone stresses at the proximal femur during gait and from the forces generated by a fall [10,23,24]. These studies demonstrate that stresses increase in areas of the bone that are structurally weak, but they do not explain why bones become weak in the first place. Femoral stress, an index of modeling response, may provide some insight into why some older adults have weaker bones. Third, our study builds on previous research by attempting to identify individuals with a reduced modeling response based on an algorithm using widely available data. The engineering model we used for these analyses relies on DXA data that is widely available on individuals participating in large cohort studies and clinical trials using HSA, a technique for deriving bone structural properties from two dimensional data that has been employed in numerous studies [25-32].

Despite these strengths, there are several limitations. First, our measure of femoral stress involves assumptions about the magnitude and direction of the forces generated in a one legged stance. In addition, the engineering model of the hip was restricted to the frontal plane, and the forces on the hip in ambulation are frequently directed out of the frontal plane. However, current methods for a more complex three dimensional model require computed tomography, which was only available for a small subset of individuals in this

study. Second, we may not have adequately captured all aspects of load in our attempt to approximate muscle loading forces. A direct measure of physical activity would be a valuable addition to this analysis, but the self-report measure of physical activity available was minimally correlated with femoral stress, percent lean mass and body mass adjusted knee strength, so it appeared insufficient to assess these relationships. Third, we assumed that whole body lean mass and leg muscle strength are proportional to the forces generated at the hip. Our measure of muscle strength relied on knee extension strength, and although knee extension strength involves thigh muscles that also function in ambulation, it is not a direct evaluation of hip forces per se. We utilized total lean mass based on whole body DXA scans, which should be greater in more active individuals. However, lean mass may not be evenly distributed throughout the body, and we were unable to measure the muscle regions that most directly determine maximal muscle force at the hip. Fourth, despite our best efforts to ensure that the association between our lean mass and muscle strength measure with femoral stress was not merely due to their associations with weight (by dividing lean mass and strength by body mass), there is always the chance of residual confounding due to model misspecification. Fifth, the cross sectional nature of the data precludes evaluation of causal relationships. Finally, if there are birth cohort effects related to lifetime patterns of body composition and physical activity, these results might not apply to older adults in other, more recent cohorts. For example, older adults today were likely to become over-weight or obese at earlier ages resulting in a longer lifetime exposure to excess weight [33].

In conclusion, results from this study provide insight into bone modeling differences as measured by femoral stress. Greater lean mass is associated with less femoral stress, indicating that the measure captures elements of bone's response to load. Variation in femoral stress after accounting for lean mass and knee strength, which was independently associated with femoral stress in women, may provide an indicator of heterogeneity in the modeling response to load. Femoral stress as it is currently estimated does not have clinical applications, per se, but it allows us to investigate a potentially important mechanism of bone fragility using existing data from large prospective studies and provides a platform for future research into the important relationship between muscle and bone. Many studies have shown that muscle is positively associated with bone and therefore building or maintaining muscle should have positive effects on bone. However if individuals have a deficient modeling response to muscle load, then it is unclear whether interventions aimed at building muscle, will have the desired effect. Future research on femoral stress should consider incorporating an assessment of muscle loading forces.

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Fig. 1. Study sample. Data presented in this analysis represent 2539 men and women ages 70–79 enrolled in the Health ABC study (83% of all patients enrolled) with complete information on body composition and key indicators of health collected during the first study visit.

Fig. 2.

Estimating femoral stress. W_1 refers to body weight, F_m to the abductor muscle force, and F_j to the joint force at the femoral head. NL = Neck Length; d = distance from the center of mass; TL = distance from the weight vector to the outer surface of the greater trochanter; SL = shaft length is computed from forensic formula on height: a = neck shaft angle from HSA; $\beta = 10$ degrees; $\theta = 19$ degrees. A detailed description of the stress calculation is included in the Appendix.

Table 1

Selected baseline characteristics for 2539 men and women by quartile of femoral stress.

	Men (<i>n</i> = 1252)				Women (<i>n</i> = 1287)				<i>P</i>	
	Q1 (Low)	Q2	Q3	Q4 (High)	Q1 (Low)	Q2	Q3	Q4 (High)		
Femoral stress and its components										
Femoral stress (MPa), mean (range)	6.29 (3.41-7.01)	7.50 (7.02-7.96)	8.39 (7.96-8.90)	9.88 (8.90-14.88)	-	7.37 (3.88-8.22)	8.78 (8.23-9.32)	9.91 (9.33-10.56)	11.97 (10.57-17.49)	-
HHHeight Height (cm), mean (SD)	173.12 (6.61)	172.74 (6.57)	173.51 (6.27)	174.32 (6.64)	-	159.29 (5.91)	159.41 (6.22)	159.17 (5.88)	160.55 (6.03)	-
Weight, kg (mean, SD)	76.1 (12.5)	79.4(11.6)	81.5 (11.7)	88.5 (13.4)	-	623 (11.5)	67.5 (12.5)	71.7 (13.0)	80.1 (14.8)	-
Narrow neck BMD (g/cm); mean (SD)	D.95 (0.18)	0.87 (0.14)	0.82 (0.14)	0.77 (0.14)	-	0.80 (0.16)	0.75 (0.15)	0.72 (0.13)	0.69 (0.12)	-
Narrow neck CSA (g/cm ²); mean (SD)	332 (0.67)	2.94 (0.48)	2.77 (0.43)	2.59 (0.44)	-	2.42 (0.49)	2.24 (0.45)	2.14 (0.39)	2.06 (0.36)	-
Narrow neck CSMI, (g/cm ⁴), mean (SD)	3.76 (1.17)	3.13 (0.73)	2.91 (0.63)	2.72 (0.64)	-	2.02 (0.56)	1.82 (0.50)	1.70 (0.42)	1.62 (0.39)	-
Covariates										
Age, years, mean (SD)	73.9 (2.8)	73.6 (2.9)	73.6 (2.9)	73.7 (2.9)	0.419	73.7 (2.9)	73.5 (2.9)	73.2 (2.7)	733 (2.7)	0.054
Race (% white)	58.8	67.1	67.4	65.2	0.107	59.9	59.6	50.6	483	<0.001
Health status										
Number of 7 co-morbidities (mean; range)	0.57 (0-3)	0.59 (0-3)	0.60 (0-4)	0.58 (0-5)	0.699	0.49 (0-4)	0.55 (0-4)	0.47 (0-3)	0.52 (0-4)	0.946
General health status (%)										
Excellent/very good	46.0	49.5	54.3	42.5		44.1	44.4	46.9	39.9	0.112
Good	34.8	35.1	35.8	403		45.0	43.5	34.2	44.2	
Fair/poor	19.2	15.3	10.9	173		10.9	12.1	18.9	15.9	
# of medications mean, (SD)	2.80 (2.8)	2.54 (2.6)	2.61 (2.5)	2.83 (2.4)	0.225	3.06 (2.6)	3.19 (2.7)	3.35 (2.6)	3.06 (2.7)	0.852
Alcohol use, <i>n</i> (%)										
1-3 drinks/week	230 (73.5)	238 (76.0)	230 (73.5)	237 (75.7)	0.560	276 (85.7)	282 (87.6)	292 (90.7)	287 (89.4)	0.073
4-6 drinks/week	67 (21.4)	64 (20.4)	75 (23.9)	69 (22.0)		44 (13.7)	37 (11.5)	30 (9.3)	33 (103)	

	Men (<i>n</i> = 1252)					Women (<i>n</i> = 1287)					<i>P</i>
	Q1 (Low)	Q2	Q3	Q4 (High)	<i>P</i>	Q1 (Low)	Q2	Q3	Q4 (High)	<i>P</i>	
7 + drinks/week	16(5.1)	11 (3.5)	8 (2.6)	7 (2.2)		2 (0.6)	3 (0.9)	0	1 (0.3)		
Smoking, <i>n</i> (%)											
No	92 (29.4)	101 (323)	82 (26.2)	93 (29.7)	0.657	186 (57.8)	185 (57.5)	184(57.1)	178 (55.5)		0.558
Yes	221 (70.6)	212 (67.7)	231 (73.9)	220 (70.3)		136 (42.4)	137 (42.6)	138 (42.8)	143 (44.6)		
Walking ability, <i>n</i> (%)											
Difficult	132 (42.2)	123 (403)	136 (43.5)	167 (53.4)		175 (54.4)	186 (57.8)	213 (66.2)	212 (66.0)		<0.001
Very easy	181 (57.8)	187 (59.7)	177 (56.6)	146 (46.5)		147 (45.6)	136 (42.2)	109 (33.9)	109 (33.9)		
Mechanical load											
Percent lean mass; mean %, (SD)	69.8 (4.7)	67.9(4.1)	67.1 (4.3)	64.9 (4.1)	<0.001	59.8 (5.7)	57.7 (4.7)	55.7 (4.7)	53.5 (4.4)		<0.001
Total body mass adjusted knee strength mean, (SD)	; 1.49 (0.36)	1.44 (0.35)	1.45 (0.38)	1.34 (0.34)	<0.001	1.09(0.29)	1.08 (0.29)	1.02 (0.28)	0.93 (0.27)		<0.001

MPa = pascals; BMD = bone mineral density; CSA = cross sectional area; CSMI = cross sectional moment of inertia; number of co-morbidities from the following: osteoarthritis, angina, MI, CHF, stroke, diabetes, and COPD. Percent total body lean mass = total body lean mass (kg)/total body mass (kg); Total leg mass adjusted knee strength = isokinetic knee strength (Nm)/Total body mass (kg).

Association between percent total body lean mass, total body adjusted knee strength and femoral stress among men and women.

Percent total body lean mass = total body lean mass (kg)/total body mass (kg); Total leg mass adjusted knee strength = isokinetic knee strength (Nm)/total body mass (kg).

Model 4: Linear regression; models include percent lean mass, body mass adjusted knee strength, clinical site and the following covariates: age, race, number of comorbidities, health status, number of medications taken, alcohol use, smoking and walking ability.

Table 3

Association between percent total body lean mass, total body adjusted knee strength and femoral stress among stratified by BMI ($n = 1252$).

	Model 1		Model 2		Model 3		Model 4	
	B (95% CI)		B (95% CI)		B(95%CI)		B(95%CI)	
	Percent lean mass	Knee strength	Percent lean mass	Knee strength	Percent lean mass	Knee strength	Percent lean mass	Knee strength
Underweight ^a								
Normal ($n = 379$)	-0.1064 (-0.138, -0.074)	-	-	-0.4627 (-0.807, -0.118)	-0.103 (-0.137, -0.069)	-0.106 (-0.457, 0.243)	-0.101 (-0.136, -0.06)	-0.119 (-0.479, 0.242)
Overweight ($n = 598$)	-0.072 (-0.099, -0.044)	-	-	-0.266 (-0.560, 0.028)	-0.0715 (-0.102, -0.041)	-0.007 (-0.316, 0.302)	-0.0728 (-0.104, -0.041)	-0.068 (-0.388, 0.251)
Obese ($n = 268$)	-0.109 (-0.160, -0.058)	-	-	-0.109 (-0.664, 0.444)	-0.120 (-0.175, -0.066)	0.329 (-0.242, 0.901)	-0.102 (-0.159, -0.045)	0.278 (-0.312, 0.869)

^aThere were only 7 men that were underweight; models not generated.

Table 4

Association between percent total body lean mass, total body adjusted knee strength and femoral stress among women stratified by BMI ($n = 1287$).

	Model 1			Model 2			Model 3			Model 4		
	B (95% CI)			B (95% CI)			B (95% CI)			B (95% CI)		
	Percent lean mass	Knee strength		Percent lean mass	Knee strength		Percent lean mass	Knee strength		Percent lean mass	Knee strength	
Underweight ^a												
Normal ($n = 405$)	-0.063 (-0.094, -0.032)	-	-	-	-0.129 (-0.591, 0.332)	-	-0.064 (-0.096, -0.032)	0.104 (-0.364, 0.572)	-	-0.067 (-0.099, -0.034)	0.093 (-0.389, 0.576)	-
Overweight ($n = 484$)	-0.122 (-0.162, -0.082)	-	-	-	-0.275 (-0.835, 0.284)	-	-0.126 (-0.168, -0.085)	0.214 (-0.349, 0.778)	-	-0.128 (-0.171, -0.085)	0.199 (-0.393, 0.791)	-
Obese ($n = 372$)	-0.116 (-0.171, -0.061)	-	-	-	-1.27 (-2.06, -0.499)	-	-0.099 (-0.156, -0.043)	-0.922 (-1.72, -0.128)	-	-0.093 (-0.151, -0.035)	-0.867 (-1.69, -0.035)	-

Percent total body lean mass = total body lean mass (kg)/total body mass (kg); Total leg mass adjusted knee strength = isokinetic knee strength (Nm)/total body mass (kg).

Model 1: Linear regression models adjusted for clinical site only.

Model 2: Linear regression models adjusted for clinical site only.

Model 3: Linear regression; models include percent lean mass, body mass adjusted knee strength and clinical site.

Model 4: Linear regression; models include percent lean mass, body mass adjusted knee strength, site and the following covariates: age, race, number of comorbidities, health status, number of medications taken, alcohol use, smoking and walking ability.

^aThere were only 26 women that were underweight; models not generated.