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Relationship of Obesity with Osteoporosis

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Context: The relationship between obesity and osteoporosis has been widely studied, and epidemiological evidence shows that obesity is correlated with increased bone mass. Previous analyses, however, did not control for the mechanical loading effects of total body weight on bone mass and may have generated a confounded or even biased relationship between obesity and osteoporosis.

Objective: The objective of this study was to reevaluate the relationship between obesity and osteoporosis by accounting for the mechanical loading effects of total body weight on bone mass.

Methods: We measured whole body fat mass, lean mass, percentage fat mass, body mass index, and bone mass in two large samples of different ethnicity: 1988 unrelated Chinese subjects and 4489 Caucasian subjects from 512 pedigrees. We first evaluated the Pearson correlations among different phenotypes. We then dissected the phenotypic correlations into genetic and environmental components with bone mass unadjusted or adjusted for body weight. This allowed us to compare the results with and without controlling for mechanical loading effects of body weight on bone mass.

Results: In both Chinese and Caucasian subjects, when the mechanical loading effect of body weight on bone mass was adjusted for, the phenotypic correlation (including its genetic and environmental components) between fat mass (or percentage fat mass) and bone mass was negative. Further multivariate analyses in subjects stratified by body weight confirmed the inverse relationship between bone mass and fat mass, after mechanical loading effects due to total body weight were controlled.

Conclusions: Increasing fat mass may not have a beneficial effect on bone mass. **(*J Clin Endocrinol Metab* 92: 1640–1646, 2007)**

OBESITY AND OSTEOPOROSIS are two common complex diseases. Both have multifactorial etiologies, including genetic and environmental components, with potential interactions between them. Obesity is a condition of excessive body fat that causes or exacerbates several public health problems. Body mass index (BMI) is widely used as an index of the degree of obesity, primarily because it is easy to measure, but it cannot be used to distinguish body fat from lean mass. Consequently, more refined phenotypes have been proposed for studying obesity such as fat mass, lean mass, and percentage fat mass (PFM). Osteoporosis is a skeletal disease characterized by a reduction in bone mass; it is typically defined in an individual with a bone mineral density (BMD) T-score that is 2.5 or more SD values below normal (T-score −2.5 or less) (1).

Extensive epidemiological data show that high body weight or BMI is correlated with high bone mass and that reductions in body weight may cause bone loss (2–4). The basic mechanism underlying this observed correlation remains unclear, although several explanations have been proposed. It is generally accepted that a larger body mass imposes a greater mechanical loading on bone and that bone mass increases to accommodate the greater load. Furthermore, adipocytes are important sources of estrogen production in postmenopausal women, and estrogen is known to inhibit bone resorption by osteoclasts. It has been proposed that increases in adipose tissue with increasing BMI in postmenopausal women result in increased estrogen production, osteoclast suppression, and a resultant increase in bone mass (5). Finally, obesity has been associated with insulin resistance characterized by high plasma levels of insulin. High plasma insulin levels may contribute to a variety of abnormalities, including androgen and estrogen overproduction in the ovary and reduced production of SHBG by the liver. These changes may result in elevated sex hormone levels leading to increased bone mass due to reduced osteoclast activity and possibly increased osteoblast activity (6).

Epidemiological correlation between obesity and bone mass may be explained, in part, by the mechanisms presented previously, but further analysis reveals a much more complex relationship (7). For example, leptin, an adipocyte-secreted peptide that regulates appetite and energy expenditures, is found to have complex effects on bone. A recent study reported that leptin-deficient and leptin receptor-deficient mice had increased bone formation and that intracerebroventricular infusion of leptin causes bone loss in leptin-deficient and wild-type mice (8). Based on these observations, it was proposed that leptin may inhibit bone formation (8). In contrast to these findings, however, systemic administration of leptin to leptin-deficient mice and

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Abbreviations: BMD, Bone mineral density; BMI, body mass index; DXA, dual x-ray absorptiometry; FN, femoral neck; LS, lumbar spine; PFM, percentage fat mass; PPAR, peroxisome proliferator-activated receptor; TB BMC, total body bone mineral content.

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wild-type mice results in increased bone growth, increased skeletal mass, and increased skeletal strength (6).

Earlier epidemiological studies investigating the relationship between obesity and osteoporosis centered on phenotypic correlations between body weight (or BMI) and bone mass and produced the generally accepted view that increased mechanical loading, associated with increased body weight, contributes to increases in bone mass (9). One potential problem with these phenotypic studies is that the correlation between body weight (or BMI) and bone mass may not necessarily represent a correlation between obesity *per se* and osteoporosis, because it is excessive fat mass rather than total body weight that defines obesity. Body weight is a heterogeneous phenotype consisting of fat, lean muscle, and bone mass. Fat mass accounts for approximately 16 and 25% of total body weight in normal-weight men and women, respectively; the majority of the remaining body composition is lean mass (10). Although several previous studies (6) have used fat mass to assess the correlation between obesity and bone mass, they generally did not adjust for the mechanical loading effects of body weight on bone mass. Thus, conclusions from these studies about the relationship between obesity and bone mass may be confounded by the mechanical loading effects of total body weight on the skeletal system. Therefore, a critical question arises: what is the correlation between obesity *per se* and osteoporosis? To investigate the relationship between obesity and bone mass fully, it is necessary to control for the mechanical loading effects of total body weight in the analyses.

In the present study, using both Chinese and Caucasian populations, we found that body fat mass is negatively correlated with bone mass when the mechanical loading effect of body weight is statistically removed. Our results have important clinical implications because they suggest that interventions or treatments reducing obesity may increase bone mass and thus protect against osteoporosis.

Subjects and Methods

Subjects

The study population consisted of two samples. The first sample was composed of 1988 healthy unrelated Chinese (Han) subjects [878 premenopausal women and 1110 men; age, 27.2 ± 4.5 yr (mean ± SD); range, 19.6–45.1 yr] who were recruited in the People's Republic of China. The second sample came from the United States and consisted of 512 pedigrees with 4489 Caucasian subjects [2667 females and 1822 males; age, 47.8 ± 16.2 yr (mean ± SD); range, 19.1–90.1 yr]. All the subjects signed informed consent documents before entering the studies. We adopted an exclusion criterion elaborated elsewhere (11). In brief, subjects with diseases, treatments, or conditions that would be apparent and nongenetic causes for abnormal bone mass or fat mass were excluded.

Measurement

BMD (grams per square centimeter) at the lumbar spine (LS) and femoral neck (FN), total body bone mineral content (TB BMC), fat mass, and lean mass (both in kilograms) were measured by Hologic DXA scanners (Hologic Corp., Waltham, MA). PFM is the ratio of fat mass divided by total body weight (*i.e.* the sum of fat mass, lean mass, and bone mass). For the LS BMD, the quantitative phenotype used here was combined BMD of L1–L4. Weight was measured in light indoor clothing using a calibrated balance beam scale, and height was measured using a calibrated stadiometer. BMI was calculated as weight (in kilograms) divided by height (in meters) squared.

In this study, all the subjects completed a nurse-administered risk factor questionnaire to assess information concerning smoking, physical activity, menopausal status, *etc.* The ages of starting and stopping smoking and the average packs of cigarettes smoked per day were recorded. Study subjects were classified as smokers and nonsmokers (defined as those who never smoked or had stopped smoking for at least 5 yr), with smokers numerically coded as 1 and nonsmokers as 0. For physical activity, the number of episodes of exercise per week was recorded. The regular exercisers were defined as those who exercised at least once per week and were coded as 1; nonexercisers were coded as 0 in the data analyses. Menopause status was coded as 0 and 1 for premenopause and postmenopause, respectively, and was coded as missing for males.

Statistical analyses

For the Caucasian sample, we first identified 1085 unrelated subjects [age, 62.13 ± 10.84 yr (mean ± SD)] from the 512 Caucasian pedigrees by selecting the founders and married-in subjects. Many factors such as age, sex, height, menopause status, exercise, and smoking may have significant effects on both obesity-related phenotypes and bone mass. Their significance was tested, and those significant factors were modeled as covariates in regression models. The selection of covariates was based on whether the variable was statistically significant at the significance level of $P < 0.05$. Because of the mechanical loading effect of body weight on bone mass, the true relationship between bone mass and fat mass may be confounded. To address this issue, in our regression model, we incorporated total body weight as a covariate to adjust for bone mass. By adopting this model, the mechanical loading effect of body weight on bone mass is eliminated, and the relationship between bone mass and fat mass investigated here is not confounded. In genetic analyses, adjustment for significant covariates can generally increase the genetic signal-to-noise ratio by decreasing the proportion of the residual phenotypic variation attributable to random environmental factors. In our analyses, BMD and obesity-related phenotypes were adjusted for significant covariates such as age, sex, height, menopause status, exercise, and smoking in regression models. The adjusted values were used for subsequent Pearson correlation analysis, and the residuals from the model were used in the data analyses. These analyses were conducted separately in Chinese samples and unrelated Caucasian samples selected from our Caucasian pedigrees.

We further dissected phenotypic correlations into genetic and environmental components by performing quantitative genetic variance decomposition analyses in the whole Caucasian sample (4489 subjects) using the program SOLAR (www.sfbr.org/solar/). The bivariate quantitative genetic analysis is a powerful method to assess directly the shared genetic and environmental effects by measuring the degree of genetic and environmental correlations between pairs of traits. It reestimated and decomposed the total phenotypic correlation ρ_P into the components due to genetic correlations (ρ_G) and environmental correlations (ρ_E) (12) that are shared among bone mass, lean mass, and fat mass. The signs of ρ_G and ρ_E indicate the directions of action of shared genetic and environmental effects on osteoporosis and obesity. To estimate the genetic correlations ρ_G and environmental correlations ρ_E for pairs of traits, one should first model the bivariate phenotype of an individual as a linear function of the individual's trait measurements. Then the matrix of kinship coefficients is generated, expressing relationships among all pairs of individuals in the pedigree. From standard quantitative genetic theories, the phenotypic variance-covariance matrix and its genetic and environmental components are then obtained. From these matrices, ρ_G and ρ_E are estimated directly, which was detailed elsewhere (13). We tested the significance of both ρ_G and ρ_E between any pair of traits by comparing the likelihood for the restricted model in which each of these parameters was constrained to zero to the likelihood for the general model in which all parameters were estimated. In this study, the significant level refers to $P \leq 0.05$ in a statistical test. In the statistical analyses, outliers that were 4 SD away from the respective averages were excluded. Natural log transformation was performed for variables that did not follow the normal distribution.

We further investigated the relationship between PFM and BMC in subgroups of 10-kg strata of body weight for the total 4489 Caucasian subjects. A linear mixed model was used with age, height, smoking, exercise, and menopause status modeled as covariates. Family relationships were modeled in the mixed model as random effects. Least squares mean of the TB BMC stratified by PFM in subgroups of 10-kg strata of

body weight in the whole Caucasian sample was plotted. In this study, only strata with 100 or more persons were included for each gender to achieve maximum statistical power.

Results

Table 1 shows the basic characteristics of the study population, which was stratified into four subgroups by race and gender. The Caucasian sample has a higher average age than the Chinese sample. Weight, height, BMI, fat mass, PFM, lean mass, FN BMD, and TB BMC differed significantly between groups ($P < 0.001$). In both Caucasian and Chinese samples, when compared with women, men had significantly higher height, weight, BMI, lean mass, LS BMD, FN BMD, and TB BMC and lower fat mass and PFM. For the same gender, Chinese had significantly lower BMI, fat mass, PFM, LS BMD, and TB BMC than the sex-matched Caucasians. This race difference remained even after adjustment for age.

Table 2 shows the covariates included in our model and the standardized regression coefficients and their significance. Only the significant variables were retained in the model. The adjusted, dependent variables were used for further Pearson correlation analyses.

Table 3 summarizes the results of the phenotypic correlation between bone mass and obesity-related phenotypes in unrelated samples of Chinese and Caucasians, respectively. The correlation results were similar for Chinese and Caucasians. In both Chinese and Caucasians, BMI and weight were positively correlated with bone mass. The results reported here are consistent with the long-held belief that subjects having larger body weight tend to have higher bone mass. When bone mass was adjusted for body weight, lean mass was consistently positively correlated with weight-adjusted bone mass ($P < 0.05$), suggesting that the effects of lean mass on bone mass are not simply due to weight. Most interestingly, fat mass and PFM were found to be inversely associated with weight-adjusted bone mass ($P < 0.01$) (Table 3, results presented in *parentheses*), suggesting that higher fat mass (or PFM) does not increase bone mass when the mechanical loading effects of overall body weight are statistically controlled.

The results of genetic and environmental correlations between obesity-related phenotypes and weight-adjusted bone mass are summarized in Table 4. When bone mass was adjusted for body weight, both genetic (ρ_G) and environmental (ρ_E) correlations between lean mass and weight-adjusted bone mass were significantly positive ($P < 0.01$). In contrast to these findings, fat mass and PFM were negatively associated with weight-adjusted bone mass both genetically and environmentally ($P < 0.01$). This is consistent with the results of our Pearson correlation (phenotypic correlation) analyses presented in Table 3. Our results contrast with those of previous studies suggesting that higher fat mass (*i.e.* higher obesity risk) contributes to an increase in bone mass. These results indicate that, under the same conditions of mechanical loading, a higher fat mass tends to decrease bone mass.

We further investigated the relationship of fat mass to bone mass in subjects matched by body weight. We divided the Caucasian sample into 10-kg strata of body weight. Five strata for females (50–99 kg) and four strata for males (70–109 kg) were identified, with each stratum having more than 100 subjects. For each stratum, the samples are equally divided into three subgroups according to their PFM. Figure 1 plots the least squares means and SE values of TB BMC for the low, medium, and high PFM subgroups from each of the different weight strata. Significant negative associations ($P < 0.001$) between PFM and TB BMC were found in all weight strata for both males and females.

Discussion

The key finding of this study is that fat mass (or PFM) is inversely correlated with bone mass genetically, environmentally, and phenotypically when the mechanical loading effects of body weight on bone mass are controlled. These results suggest that 1) body fat mass *per se* does not have protective effects on bone mass, and 2) shared genetic and environmental factors may have beneficial effects on reducing both obesity (by reducing body fat mass) and osteoporosis. We also found positive correlations between lean mass and bone mass regardless of adjustments for body weight, suggesting that the effects of lean mass on bone mass are not entirely attributable to the mechanical loading aspect of body weight. A straightforward explanation for this latter finding is that larger lean mass is related to larger muscles, which typically convey larger or more frequent mechanical loading to the skeleton. Our results thus support the well-known beneficial effects of mechanical loading on bone but challenge current thinking that fat mass protects against osteo-

TABLE 1. Descriptive characteristics by sex and race (mean ± SD) in the unrelated sample

	Caucasian		Chinese		Comparison[a]
	Women (1) (n = 547)	Men (2) (n = 538)	Women (3) (n = 878)	Men (4) (n = 1110)	
Age (yr)	62.04 ± 11.37	62.25 ± 10.41	27.26 ± 4.83	27.16 ± 4.18	3, 4 < 1, 2
Body weight (kg)	73.64 ± 15.51	91.01 ± 15.01	50.74 ± 6.20	62.58 ± 8.58	3 < 4 < 1 < 2
Height (m)	1.62 ± 0.07	1.77 ± 0.07	1.58 ± 0.05	1.69 ± 0.05	3 < 1 < 4 < 2
BMI (kg/m^2)	28.05 ± 5.64	29.02 ± 4.24	20.26 ± 2.28	21.81 ± 2.73	3 < 4 < 1 < 2
Fat mass (kg)	28.90 ± 9.72	24.92 ± 7.74	13.79 ± 3.6	10.52 ± 4.77	4 < 3 < 2 < 1
PFM (%)	0.38 ± 0.06	0.27 ± 0.05	0.26 ± 0.05	0.16 ± 0.05	4 < 3 < 2 < 1
Lean mass (kg)	43.31 ± 6.49	63.06 ± 8.35	36.59 ± 3.61	51.27 ± 5.22	1 < 3 < 4 < 2
Spine BMD (g/cm^2)	0.98 ± 0.16	1.08 ± 0.17	0.94 ± 0.10	0.98 ± 0.11	3 < 1, 4 < 2
FN BMD (g/cm^2)	0.74 ± 0.12	0.82 ± 0.14	0.78 ± 0.09	0.88 ± 0.12	1 < 3 < 2 < 4
TB BMC (kg)	2.09 ± 0.36	2.78 ± 0.43	1.87 ± 0.23	2.27 ± 0.29	3 < 1 < 4 < 2

[a] $P < 0.001$.

TABLE 2. The independent contribution of each confounding variable to bone mass or obesity-related phenotypes by multivariate linear regression analysis

	Standardized regression coefficient					
	Age (yr)	Sex	Height (m)	Exercise	Smoking	Menopausal status
Chinese						
Fat mass (kg)	0.242[c]	0.491[c]	0.195[c]	0.028	0.028	
Lean mass (kg)	0.088[c]	−0.517[c]	0.455[c]	0	−0.007	
PFM (%)	0.160[c]	0.677[c]	−0.034[c]	0.018	0.029	
LS BMD (g/cm^2)	0.053[a]	0.071[a]	0.320[c]	0.019	−0.050[a]	
FN BMD (g/cm^2)	−0.073	−0.230[c]	0.254[c]	0.024	−0.029	
TB BMC (kg)	0.014	−0.087[b]	0.430[c]	0.030[a]	−0.011	
Caucasians						
Fat mass (kg)	0.062	0.460[c]	0.285[c]	−0.219[c]	0.004	−0.027
Lean mass (kg)	−0.086[c]	−0.460[c]	0.446[c]	−0.067[b]	−0.013	−0.004
PFM (%)	0.124[c]	0.691[c]	−0.005	−0.147[c]	0.006	0.007
LS BMD (g/cm^2)	−0.01	0.164[c]	0.206[c]	0.041[a]	0.055[a]	−0.325[c]
FN BMD (g/cm^2)	−0.290[c]	0.026	0.251[c]	0.026	0.04	−0.147[a]
TB BMC (kg)	−0.118[c]	−0.164[b]	0.511[c]	0.046[a]	0.022	−0.137[b]

[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$.

porosis. Indeed, some earlier studies have shown that excess adipose tissue may not protect against fracture (14–17). In a study of a large cohort of Chinese by Hsu *et al.* (16), given a certain body weight, a negative relationship between fat mass and bone mass was found, and the risks of osteoporosis, osteopenia, and nonspine fractures were significantly higher for subjects with higher percentage body fat independent of body weight.

The negative genetic correlation ρ_G between fat mass and weight-adjusted bone mass suggests that fat and bone mass share some common genetic factors and molecular pathways that appear to have opposite effects on fat *vs.* bone mass. This finding is consistent with our current understanding of the differentiation of adipose tissue and the skeleton. Adipocytes and osteoblasts originate from a common progenitor, pluripotential mesenchymal stromal cells, and their differentiation is regulated through the peroxisome proliferator-activated receptor (PPAR)-γ pathway (18). Activation of PPAR-γ drives the differentiation of mesenchymal stromal cells toward adipocytes over osteoblasts (19). A set of factors common to osteogenesis and adipogenesis determines the entry of mesenchymal stromal cells into different functional stages (20). For example, bone morphogenetic protein and retinoic acid may cooperate to induce osteoblast differentiation of preadipocytes (21). Molecular genetic studies have also identified some candidate genes that have common effects on osteoporosis and obesity. Such genes include IGF-I, IGF-II, LEPR, NPY, VDR, ER-α, AR, TGF-β1, IL-6, TNF-α, TNFR2, ApoE, and PPAR-γ. For instance, the Pro10 allele in the TGF-β1 gene was found to reduce the risk of both obesity (22) and osteoporosis (23).

Our current study also found a negative environmental correlation between fat mass and weight-adjusted bone mass. This implies that fat and bone mass share some environmental factors, which may alleviate the risk of both obesity and osteoporosis. Several lines of evidence support our observations here. For instance, physical exercise may prevent body fat accumulation while increasing bone mass (24). Milk and tea are believed to be beneficial for the prevention of both osteoporosis and obesity (25). Milk is a good source of highly absorbable calcium, and increased milk intake may increase peak bone mass in puberty and slow bone loss and reduce the incidence of osteoporotic fracture in the elderly (26). Studies also show that high calcium intake may promote weight or fat loss (27), although long-term trials are needed to confirm such observations.

TABLE 3. The phenotypic correlation between obesity-related phenotypes and bone mass in 1988 unrelated Chinese and 1085 unrelated Caucasians with bone mass unadjusted *vs.* adjusted for weight

	LS BMD (g/cm^2)	FN BMD (g/cm^2)	TB BMC (kg)
Chinese			
Fat mass (kg)	0.09[b] (−0.12[b])	0.13[b] (−0.12[b])	0.16[b] (−0.23[b])
Lean mass (kg)	0.35[b] (0.15[b])	0.38[b] (0.16[b])	0.61[b] (0.29[b])
PFM (%)	0.02 (−0.16[b])	0.05[a] (−0.15[b])	0.02 (−0.30[b])
BMI (kg/m^2)	0.25[b]	0.29[b]	0.43[b]
Weight (kg)	0.32[b]	0.34[b]	0.57[b]
Caucasians			
Fat mass (kg)	0.13[b] (−0.12[b])	0.24[b] (−0.13[b])	0.04 (−0.48[b])
Lean mass (kg)	0.40[b] (0.10[a])	0.52[b] (0.09[a])	0.80[b] (0.36[b])
PFM (%)	−0.14[b] (−0.17[b])	−0.12[b] (−0.18[b])	−0.46[b] (−0.65[b])
BMI (kg/m^2)	0.24[b]	0.36[b]	0.25[b]
Weight (kg)	0.36[b]	0.51[b]	0.63[b]

Values in *parentheses* were the standardized regression coefficients when bone mass was adjusted for body weight.
[a] $P < 0.05$.
[b] $P < 0.01$.

TABLE 4. The genetic and environmental correlations between obesity-related phenotypes and weight-adjusted bone mass inferred from the whole sample in Caucasians

		LS BMD (g/cm^2)	FN BMD (g/cm^2)	TB BMC (kg)
Fat mass (kg)	ρ_G	-0.16^a	-0.23^a	-0.51^a
	ρ_E	-0.17^a	-0.28^a	-0.65^a
Lean mass (kg)	ρ_G	0.33^a	0.28^a	0.70^a
	ρ_E	0.21^a	0.16^a	0.56^a
PFM (%)	ρ_G	-0.23^a	-0.32^a	-0.56^a
	ρ_E	-0.20^a	-0.30^a	-0.58^a

ρ_G (genetic correlation) is the correlation due to genes shared by bone mass and obesity. ρ_E (environmental correlation) is the correlation due to shared environmental factors. *P* values were estimated by comparison with the likelihood of a nested model in which either ρ_G or ρ_E was fixed at zero (for ρ_G and ρ_E, respectively).

[a] $P < 0.01$.

Our results may have important clinical implications. First, a person may gain bone mass without having to gain fat mass. Second, medical interventions or lifestyle modifications may be favorable for the protection of both osteoporosis and obesity. Indeed, a few studies have suggested such effects. For instance, menopause is associated with increased bone loss, increased fat mass, and decreased lean mass. Hormone replacement therapy has been proven to be efficient in attenuating bone loss in postmenopausal women (28) and reversing menopause-related obesity and loss of lean mass (29). Leptin, a key factor regulating appetite and body weight, has been shown to influence bone mass (30). Treatment of children with congenital leptin deficiency with recombinant leptin leads to increased bone mass (31) and a sustained reduction in weight, predominantly as a result of a loss of fat (30, 31). However, Ducy *et al.* (8) and Takeda *et al.* (32) reported that leptin may decrease bone formation through the sympathetic nervous system, indicating that the effect of leptin on bone mass is complex (33). Other medical interventions have also been shown to have adverse effects on health, leading to both osteoporosis and obesity. For example, osteoporosis and obesity are the two main side effects of treatment with GnRH agonists, agents that are used for treating nonmetastatic prostate cancer (34).

We acknowledge that our study is cross-sectional in nature instead of a longitudinal design. Therefore, in this study, the relationship between bone mass and obesity-related phenotypes is descriptive and might be confounded by cohort effects. However, the age range of our Chinese sample is narrow, which may suggest that cohort effects, if any, may

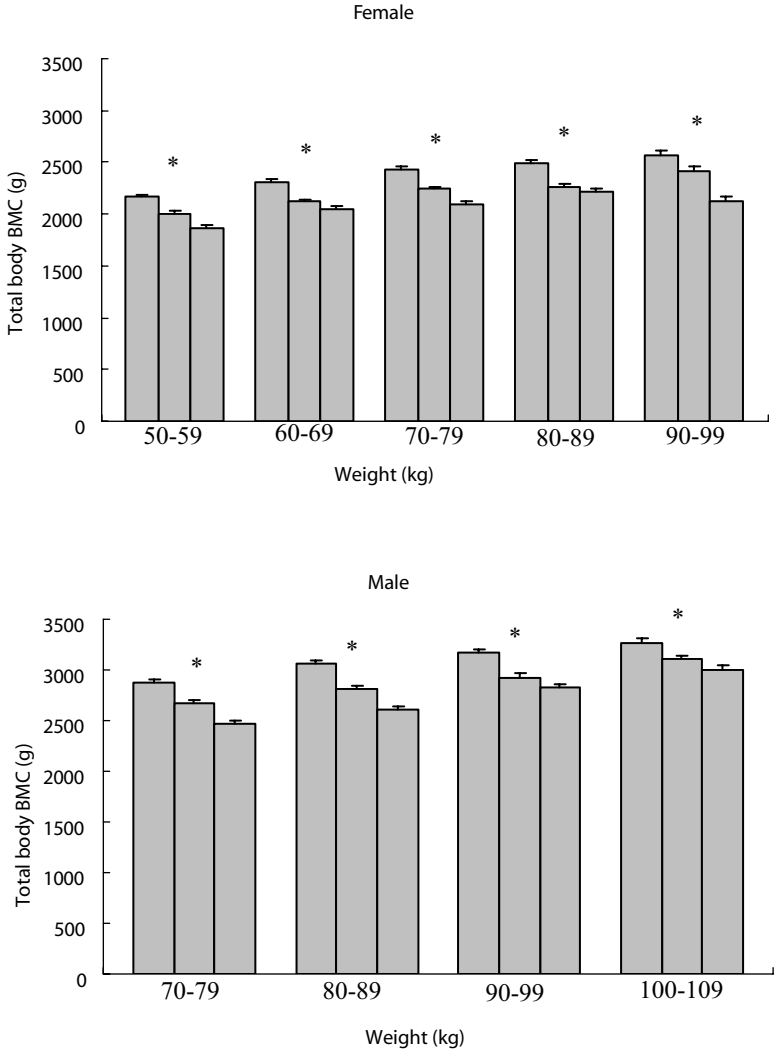

FIG. 1. Least-squares mean (±SE) of the TB BMC stratified by PFM in 10-kg strata of body weight in 4489 Caucasians. Each *bar* in each body weight stratum represents one third of the population with the lowest, middle, and highest (*left to right*) PFM. A linear mixed model was used with age, height, exercise, and menopause status as covariates. Familial relationships were treated as random effects in the model. *, $P < 0.0001$.

be relatively small. Future longitudinal studies will be helpful in clarifying the relationship regarding changes of bone mass and fat mass.

It should also be noted that the statistically significant correlations reported here only imply an overall effect of the shared factors in determination of fat and bone mass. Some individual factors may not follow this correlation. For example, smoking is associated with low bone mass and accelerated bone loss (35), but it may also reduce BMI (36).

An additional concern with this study is that the observed negative correlation between fat mass and weight-adjusted bone mass might be an artifact caused by dual energy x-ray absorptiometry (DXA) measurement. It is likely that heterogeneous distributions of soft tissues could lead to systematic inaccuracies inherent to DXA-derived BMD measurements. Changes of fat distribution can cause alterations in bone measurement without any real change in the skeleton (37, 38). However, in this study, our results are not likely to be biased for the following reasons:

1) A previous analytic and quantitative simulation study indicated that decreasing fat mass by weight change always artificially led to lower BMD, and vice versa (39), which is qualitatively different from our results.

2) Prior studies (37, 38) showed that increasing fat thickness may spuriously decrease total body BMD. The spurious decrease in BMD, if due to DXA measurement, is attributable to the potential spurious increases in both BMC (numerator) and bone area (denominator for BMD) (37, 38). Bone area may have a relatively larger spurious increase than BMC, resulting in a potential spurious decrease of BMD (37, 38). However, in this study, we found a negative, rather than a positive, correlation between fat mass and weight-adjusted TB BMC, which indicates that increasing fat mass is associated with a smaller BMC. This result suggests that our finding is unlikely to be explained by an artifact of the DXA measurement, which leads to larger BMC with increasing fat. Moreover, we tested the relationship between fat mass and bone area in our two large samples. We found that fat mass was negatively correlated with weight-adjusted bone area (Table 5). This finding is qualitatively different from the positive correlation between spurious change of bone area and change of fat thickness due to DXA measurements as suggested in some earlier studies (38). This result further ensured the robustness of our results against the potential artificial effects of DXA measurement.

In summary, we found a negative correlation between fat mass (or PFM) and bone mass, both genetically and environmentally. In addition, we reaffirmed the beneficial effects of appropriate weight-bearing and mechanical loading on a healthy skeletal system.

TABLE 5. Pearson correlations between fat mass and weight-adjusted bone area in 1988 unrelated Chinese and 1085 unrelated Caucasians

		LS bone area	FN bone area	Total body bone area
Fat mass (kg)	Chinese	-0.25^a	-0.16^a	-0.22^a
	Caucasians	-0.17^a	-0.12^a	-0.15^a

^{a} $P < 0.01$.

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