

# Centrally located body fat is associated with lower bone mineral density in older Puerto Rican adults<sup>1–3</sup>

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## ABSTRACT

**Background:** Fat mass is thought to be protective against osteoporosis, primarily because of its weight-bearing effect. Few studies have evaluated the association between abdominal fat mass (AFM) and bone health beyond its weight-bearing effect.

**Objective:** We tested the hypothesis that higher body weight-adjusted AFM is associated with poor bone health.

**Design:** A cross-sectional study was conducted in 629 Puerto Rican adults aged 47–79 y. Bone mineral density (BMD) of the femoral neck, trochanter, total femur, and lumbar spine (L2-L4) were measured by using dual-energy X-ray absorptiometry (DXA). AFM and total fat mass (TFM) were assessed by using body-composition software from whole-body DXA scans. Osteoporosis and osteopenia were defined as T-scores  $\leq -2.5$  and  $-1.0$  to  $-2.5$  SD, respectively, at the respective bone site.

**Results:** After confounders were controlled for, body weight-adjusted AFM was inversely associated with BMD at all 4 bone sites in women and at the femoral neck in men. For TFM, small inverse associations were seen at the trochanter and total femur in women. In men, similar associations were seen at the 3 femur sites. In both sexes, the odds for osteoporosis or osteopenia at each of the femoral sites increased by 10–16% for every 100-g increase in body weight-adjusted AFM.

**Conclusions:** Higher AFM was associated with poor bone health in this Puerto Rican sample. Efforts to reduce abdominal obesity will not only reduce the risk of chronic disease but may also improve bone health. This trial is registered at [clinicaltrials.gov](http://clinicaltrials.gov) as NCT01231958. *Am J Clin Nutr* 2011;94:1063–70.

## INTRODUCTION

Obesity and osteoporosis are 2 major public health concerns with high prevalence rates, the latter of which disproportionately affects older adults. Osteoporosis and low bone mass affect nearly 44 million US adults aged  $\geq 50$  y (1). By 2025, annual fractures and costs are expected to rise by 50% from \$17 billion in 2005. The greatest increase in costs is estimated to be 175% for Hispanics (2), which suggests that this is a high-risk group. Likewise, the prevalence of obesity, especially abdominal obesity, remains disturbingly high among adults in the United States. Recent estimates from NHANES indicate that the prevalence of abdominal obesity among men and women has increased from 37.8% and 55.8% during 1999–2000 to 43.7% and 61.8% during 2007–2008 (3).

The prevailing view regarding the relation between fat and bone mass is that body fat protects against osteoporosis primarily

because of its weight-bearing effect on the skeleton. With the recognition of fat as an endocrine organ, the effect of fat mass on bone may extend beyond its mechanical load on the skeleton. Comparing NHANES 1999–2002 data with NHANES III data, Looker et al (4) found a positive relation between BMI and BMD<sup>4</sup> but concluded that the increasing rates of overweight among older women are not likely to lead to a significant reduction in the prevalence of osteoporosis. More recently, comparing NHANES III data with NHANES 2005–2006 data, Looker et al (5) found that the prevalence of osteoporosis at the femoral neck decreased but changes in BMI did not fully explain this decline. Whereas most of the research on the association between fat mass and BMD has focused on TFM, it is not clear how AFM is associated with bone mass. Abdominal obesity, assessed by using waist circumference, is associated with higher mortality independent of BMI (6). Furthermore, AFM is known to contribute to inflammation (7, 8), insulin resistance (9), dyslipidemia (10), metabolic syndrome (11), and hypertension (12). Given the established risks associated with AFM, it is not clear how AFM is associated with bone mass after its mechanical loading effect is controlled for, especially in an ethnic population.

Most research in Hispanics has focused on Mexican Americans, because of their majority as a Hispanic subgroup. However, Puerto Ricans are the largest Hispanic subgroup in the northeastern United States, and prior research indicates that they have established health disparities and a greater burden of chronic disease (13). The metabolic syndrome, characterized by abdominal obesity, is also high in this group (14). Yet, there is

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<sup>4</sup> Abbreviations used: AFM, abdominal fat mass; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; GED, General Education Development; TFM, total fat mass.

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a paucity of research on bone health in this population. Because the health care costs of both osteoporosis and abdominal obesity, and the associated increase in chronic disease risk, are considerable, it is crucial to understand how AFM affects BMD independent of body weight. We therefore studied this important association in a group of 629 older Puerto Rican adults ( $n = 164$  men,  $n = 465$  women), aged 47–79 y, living in the greater Boston area.

## SUBJECTS AND METHODS

### Participants

We used data from the Boston Puerto Rican Osteoporosis Study, an ancillary study to the Boston Puerto Rican Health Study, a prospective cohort study in older Puerto Ricans aged 45–75 y living in the greater Boston area. The design of the Boston Puerto Rican Health Study was described in detail elsewhere (14). Briefly, at baseline and at 2 y, bilingual interviewers visited the participants' homes and administered questionnaires to collect information on socioeconomic status, health and health behaviors, acculturation, depressive symptoms, stress, social support, usual diet, and cognitive functioning. In addition, anthropometric, blood pressure, and physical performance measures were collected. Biological samples, including saliva, urine, and 12-h fasting blood, were collected by the phlebotomist in the participants' homes on a day after the interview or as soon as possible thereafter. At the completion of the 2-y follow-up, participants reconsented to the osteoporosis study. An appointment was made for consenting participants to visit the Metabolic Research Unit at the Human Nutrition Research Center on Aging at Tufts University to undergo bone density and body-composition measurements, to have additional blood samples collected, and to complete additional questionnaires on osteoporosis medication use and sunlight exposure. Multiple attempts were made to complete this visit within 1 mo of the 2-y follow-up visit for the parent study. All questionnaires were administered by trained bilingual interviewers. By September 2010, 756 of a total of 1123 participants who completed 2-y follow-up visits consented to the osteoporosis study. Primary reasons for nonparticipation included not being interested in the osteoporosis study ( $n = 163$ ), scheduling problems ( $n = 139$ ), loss to follow-up ( $n = 33$ ), and relocation out of Massachusetts ( $n = 15$ ). Furthermore, 17 participants died since their 2-y follow-up interview. Women who declined participation were more likely to be older (61.3 compared with 59.3 y;  $P = 0.001$ ) and have higher energy-adjusted intakes of alcohol (4.5 compared with 1.5 g/d;  $P = 0.05$ ). Men who declined participation in the osteoporosis study were more likely to be older (61.6 compared with 58.4 y;  $P = 0.003$ ), to have a lower BMI (28.6 compared with 30.2;  $P = 0.03$ ), and to have a lower waist circumference (100 compared with 105 cm;  $P = 0.02$ ). No other significant differences in socio-demographic or dietary variables were found. For analyses with femoral BMD measures as the outcome, we excluded one participant with a poor-quality hip scan. At the time of analysis, complete and cleaned data were available for 629 participants (164 men and 465 women). All study protocols were approved by the Institutional Review Board of Tufts Medical Center.

## Methods

### Outcome assessment

On the basis of recommendations from the International Society for Clinical Densitometry (15), we made an a priori decision to include only BMD measurements at the femoral neck, total hip, and posterior-anterior lumbar spine (L2-L4) in all our analyses. In addition, we also included the trochanter, because inclusion of this anatomic site provides a complete picture of the hip. We measured BMD ( $\text{g}/\text{cm}^2$ ) of the femoral neck, trochanter, total hip, and lumbar spine by DXA (Lunar model Prodigy scanner; General Electric) using standard procedures. The root mean square precisions of these measurements were 0.65% for total-hip BMD, 1.03% for the trochanter, 1.31% for the femoral neck, and 1.04% for the lumbar spine (16). For femur measurements, the right hip was scanned unless there was a history of hip fracture or joint replacement. During the study, the stability of DXA measurements was determined by scanning an external standard (aluminum spine phantom; Lunar Radiation Corp) every week. On the basis of the WHO definitions, osteoporosis and osteopenia were defined as T-score thresholds of  $\geq 2.5$  or 1.0 SD, respectively, below the healthy young adult mean at the respective bone site. We reviewed all scans with T-scores  $> 4.0$  to check for extraskeletal calcification or for the presence of non-anatomic parts in the DXA scan region.

### Exposure assessment

TFM (kg) was assessed from whole-body scans. AFM (kg) was measured by using specialized regional body-composition software (ENCORE version 12.2) from whole-body DXA scans. The androidal or abdominal region of interest height was defined by the manufacturer as 20% from pelvis cut to neck cut. AFM was the weight of fat tissue in this region.

### Assessment of covariates

At the 2-y follow-up visit, information on age, sex, education, and smoking status was collected by questionnaire. Physical activity was assessed by using a modified Paffenbarger questionnaire from the Harvard Alumni Activity Survey (17, 18). Usual intakes of calcium (mg/d), alcohol (g/d), and total energy (kcal/d) were assessed by using a semiquantitative food-frequency questionnaire that was specifically developed and validated for the Puerto Rican population (19). At the osteoporosis study visit, we administered a short questionnaire to assess osteoporosis prescription medication use (yes or no), including use of bisphosphonates, calcitonin, calcium, vitamin D, and cod liver oil. Because BMD is known to vary by season in the New England area (20, 21), we created a 4-level categorical variable for season of BMD measurement as follows: July, August, and September were coded as summer; October, November, and December as fall; January, February, and March as winter; and April, May, and June as spring. Standing height was measured with a stadiometer (Seca). Weight was measured with a digital scale (model Alpha Seca). Fasting blood samples (12 h) were drawn from participants by a certified phlebotomist during the morning of the osteoporosis study visit. Blood was collected into evacuated tubes containing EDTA, and plasma was separated by immediately centrifuging at  $3421 \times g$  at  $4^\circ\text{C}$  for 15 min. Plasma 25-hydroxyvitamin D (ng/mL) was measured by using a  $^{125}\text{I}$

radioimmunoassay kit procedure (DiaSorin Inc) as specified by the manufacturer’s procedural documentation (68100E). The intra- and interassay CVs were 10.8% and 9.4%, respectively.

**Statistical analyses**

All statistical analyses were performed by using SAS version 9.2 (SAS Institute Inc). Formal hypothesis testing was 2-sided, and the nominal type I error rate was 0.05. Because distribution of central (abdominal) fat mass is sex-specific, we stratified all analyses by sex. Because body weight and AFM may be highly collinear, inclusion of both variables in a regression model may introduce multicollinearity and make the model unstable. Therefore, we first regressed AFM on body weight and saved the residuals. These residuals represent the variation in AFM that is independent of body weight. We then added the mean body weight to each of these residuals to arrive at body weight-adjusted AFM (22). Body weight-adjusted AFM was used as the primary exposure in all our analyses. Participants were divided into quartiles of body weight adjusted AFM, separately for men and women. We calculated age-adjusted means for lifestyle, socioeconomic, anthropometric, and health characteristics across increasing quartiles of body weight-adjusted AFM by using PROC GLM. Similarly, dietary intakes were examined across quartiles by using ANOVA with adjustment for age and energy intake. We assessed significance across quartiles of body weight-adjusted AFM using linear (for continuous variables) or logistic (for categorical variables) regression. Tests for linear trend were conducted by assigning each participant the median grams of body weight-adjusted AFM for each quartile category and treating this value as a continuous measure in a regression model.

We used the general linear models procedure to model associations between body weight-adjusted AFM (continuous and categorical) and BMD (continuous) of the femoral neck, trochanter, total hip, and lumbar spine. We adjusted for age (y), current smoking status (y), education (<9th grade, 9th–12th grade/GED, some college/college or graduate school), alcohol intake (g/d), calcium intake (mg/d), total energy intake (kcal/d), season of BMD measurement (spring, summer, fall, or winter), physical activity score, plasma 25-hydroxyvitamin D (ng/mL) concentration, and osteoporosis medication use (y). To adjust for confounding due to skeletal size and the mechanical loading of body weight, we additionally adjusted for height and body weight. For all linear models, we checked the assumptions of normality, linearity, and homogeneity by examining plots of residuals compared with predicted values and normal probability plots of residuals. Final models were checked for outliers and influential points by using scatter plots. All analyses were adjusted for multiple comparisons by using Dunnett’s adjustment with the lowest quartile as the reference group. To compare the magnitude of the effect sizes of AFM on BMD with those of TFM on BMD, we repeated all our analyses by replacing body weight-adjusted AFM with body weight-adjusted TFM as the main exposure variable. We used logistic regression to model the odds of either osteoporosis or osteopenia for each 100-g increase in body weight-adjusted AFM. Goodness of fit was assessed by using the Hosmer-Lemeshow test.

**RESULTS**

Fat mass around the abdominal area in Puerto Rican women in the highest quartile was nearly 1.4 times that in the lowest quartile

**TABLE 1**  
Characteristics of Puerto Rican women across quartiles of body weight-adjusted abdominal fat mass<sup>1</sup>

	Quartile of abdominal fat mass				P-trend
	1	2	3	4	
Abdominal fat mass (kg)	2.84 (1.84–3.06) <sup>2</sup>	3.25 (3.07–3.38)	3.55 (3.39–3.67)	3.92 (3.68–5.09)	
No. of subjects	116	116	117	116	
Age (y)	60.2 ± 0.7 <sup>3</sup>	60.6 ± 0.7	60.7 ± 0.7	61.1 ± 0.7	0.39
Current smoker (%) <sup>4</sup>	19.0	15.5	17.4	14.2	0.40
Alcohol intake (g/d) <sup>5</sup>	1.47 ± 0.63	2.12 ± 0.64	1.84 ± 0.66	1.58 ± 0.64	0.96
Calcium intake (g/d) <sup>5</sup>	972 ± 47	1024 ± 48	967 ± 49	951 ± 47	0.62
Plasma 25(OH)D (ng/mL) <sup>4</sup>	18.7 ± 0.7	20.3 ± 0.7	19.1 ± 0.7	18.8 ± 0.7	0.82
BMI (kg/m <sup>2</sup> ) <sup>4</sup>	33.7 ± 0.6	31.6 ± 0.6 <sup>6</sup>	31.9 ± 0.6	34.9 ± 0.6	0.22
Weight (kg) <sup>4</sup>	83.3 ± 1.6	76.2 ± 1.6	74.7 ± 1.6	81.9 ± 1.6	0.37
Height (m) <sup>4</sup>	1.57 ± 0.01	1.55 ± 0.01 <sup>7</sup>	1.53 ± 0.01 <sup>7</sup>	1.56 ± 0.01 <sup>8</sup>	<0.0001
Waist circumference (cm) <sup>4</sup>	101 ± 1	101 ± 1	101 ± 1	110 ± 1 <sup>7</sup>	<0.0001
Physical activity score <sup>4</sup>	31.4 ± 0.4	30.9 ± 0.4	31.5 ± 0.4	30.2 ± 0.4	0.08
Education (%) <sup>4</sup>					
<9th grade	38.6	59.6 <sup>8</sup>	53.0 <sup>6</sup>	55.6 <sup>6</sup>	0.02
9th–12th grade/GED	35.3	29.2	34.8	30.3	0.58
At least some college	26.2	11.2 <sup>8</sup>	12.2 <sup>8</sup>	14.1 <sup>6</sup>	0.02
Osteoporosis medication use (%) <sup>4</sup>	50.5	52.6	48.7	51.7	0.99
Total household income (US\$/y) <sup>4</sup>	19,561 ± 1869	18,543 ± 1826	16,051 ± 1826	13,678 ± 1851	0.02

<sup>1</sup> GED, General Education Development; 25(OH)D, 25-hydroxyvitamin D.

<sup>2</sup> Median; range in parentheses (all such values).

<sup>3</sup> Mean ± SEM (all such values).

<sup>4</sup> Adjusted for age by ANOVA (PROC GLM; SAS Institute).

<sup>5</sup> Adjusted for age and energy intake by ANOVA (PROC GLM).

<sup>6–8</sup> Significantly different from quartile 1: <sup>6</sup>P < 0.05, <sup>7</sup>P < 0.0001, <sup>8</sup>P < 0.01.

of body weight–adjusted AFM (**Table 1**). Median AFM values in quartiles 1, 2, 3, and 4 were 2.84, 3.25, 3.55, and 3.92 kg, respectively. Women in the highest compared with those in the lowest quartile of body weight–adjusted AFM were more likely to have lower height and higher waist circumference, less likely to be physically active, had lower educational status, and had a lower total household income than did women with the least body weight–adjusted AFM. Body weight–adjusted AFM in Puerto Rican men in the highest quartile of AFM was nearly 1.5 times that in men in the lowest quartile (**Table 2**). Median values of body weight–adjusted AFM in increasing higher quartiles were 2.38, 2.86, 3.27, and 3.64 kg, respectively. Similar to their female counterparts, these men were more likely to have lower height and higher waist circumference than men in the lowest quartile of body weight–adjusted AFM. These men were also older and were less likely to be physically active than were men with the lowest body weight–adjusted AFM.

After differences in confounders and in the mechanical loading effect of body weight and height were controlled for, body weight–adjusted AFM was negatively associated with BMD in both men and women (**Table 3**). These associations were significant at all 4 bone sites in women. In men, significant negative associations were observed only at the femoral neck. In women, body weight–adjusted TFM (kg) was significantly and negatively associated with BMD at the trochanter and total femur. In men, body weight–adjusted TFM was negatively associated with BMD at all 3 hip sites, but not at the lumbar spine. Effect sizes for body weight–adjusted TFM were much lower than those for body weight–adjusted AFM.

Among Puerto Rican women, BMD in the highest quartile of body weight–adjusted AFM for all 4 bone sites was significantly

lower than BMD in the lowest quartile ( $P$ -trend < 0.01) (**Figure 1A**). In Puerto Rican men, BMD at the 3 hip sites was lower across increasing quartiles of body weight–adjusted AFM ( $P$ -trend < 0.05). No association was seen at the lumbar spine (**Figure 1B**).

In women, the multiple adjusted ORs of osteoporosis or osteopenia at the femoral neck, trochanter, total femur, and lumbar spine for every 100-g greater body weight–adjusted AFM were 1.10 (95% CI: 1.05, 1.16), 1.13 (95% CI: 1.07, 1.19), 1.13 (95% CI: 1.06, 1.20), and 1.00 (95% CI: 0.96, 1.05), respectively (**Figure 2A**). In men, higher body weight–adjusted AFM was associated with a higher likelihood of osteoporosis or osteopenia at all 3 hip sites, but not at the lumbar spine. The ORs for osteoporosis or osteopenia at the femoral neck, trochanter, total femur, and lumbar spine for every 100-g greater AFM were 1.14 (95% CI: 1.04, 1.25), 1.16 (95% CI: 1.05, 1.28), 1.16 (95% CI: 1.04, 1.28), and 1.02 (95% CI: 0.94, 1.12), respectively (**Figure 2B**). The  $P$  value for the Hosmer-Lemeshow test statistic was >0.50, which indicated that the logistic regression model was a good fit.

## DISCUSSION

In this cross-sectional study in Puerto Rican older men and women, both body weight–adjusted AFM and TFM were inversely associated with BMD. Yet, effect sizes were much smaller for TFM than for AFM. In women, higher body weight–adjusted AFM was associated with lower BMD at all 4 bone sites. In men, this association was restricted to the femoral neck. In both sexes, the strongest associations were seen at the femoral neck. In both men and women, the likelihood of osteoporosis or

**TABLE 2**  
Characteristics of Puerto Rican men across quartiles of body weight–adjusted abdominal fat mass<sup>1</sup>

	Quartile of abdominal fat mass				<i>P</i> -trend
	1	2	3	4	
Abdominal fat mass (kg)	2.38 (1.63–2.68) <sup>2</sup>	2.86 (2.69–3.05)	3.27 (3.06–3.45)	3.64 (3.46–4.96)	
No. of subjects	41	41	41	41	
Age (y)	58.2 ± 1.2 <sup>3</sup>	59.6 ± 1.2	59.7 ± 1.2	62.0 ± 1.2	0.03
Current smoker (%) <sup>4</sup>	40.2	24.1	29.9	30.9	0.45
Alcohol intake (g/d) <sup>5</sup>	11.9 ± 5.6	9.4 ± 5.4	9.7 ± 5.5	4.0 ± 5.3	0.34
Calcium intake (g/d) <sup>5</sup>	898 ± 70	995 ± 68	838 ± 69	1052 ± 66	0.34
Plasma 25(OH)D (ng/mL) <sup>4</sup>	17.3 ± 1.0	18.5 ± 1.0	15.7 ± 1.0	17.8 ± 1.0	0.74
BMI (kg/m <sup>2</sup> ) <sup>4</sup>	29.6 ± 0.8	28.7 ± 0.8	30.7 ± 0.8	31.0 ± 0.8	0.12
Weight (kg) <sup>4</sup>	86.9 ± 2.7	80.6 ± 2.6	84.4 ± 2.6	84.9 ± 2.6	0.77
Height (m) <sup>4</sup>	1.72 ± 0.01	1.67 ± 0.01 <sup>6</sup>	1.66 ± 0.01 <sup>7</sup>	1.65 ± 0.01 <sup>7</sup>	<0.0001
Waist circumference (cm) <sup>4</sup>	103 ± 2	101 ± 2	105 ± 2	108 ± 2	0.04
Physical activity score <sup>4</sup>	33.4 ± 0.8	32.4 ± 0.8	31.0 ± 0.8	30.6 ± 0.8 <sup>8</sup>	0.009
Education (%) <sup>4</sup>					
<9th grade	50.3	51.5	42.6	44.4	0.46
9th–12th grade/GED	36.0	38.9	45.0	34.9	0.89
At least some college	13.9	9.6	12.4	18.0	0.59
Osteoporosis medication use (%) <sup>4</sup>	19.8	26.9	22.6	16.7	0.70
Total household income (US\$/y) <sup>4</sup>	21,768 ± 3455	17,357 ± 3439	16,768 ± 3485	19,274 ± 3458	0.56

<sup>1</sup> GED, General Education Development; 25(OH)D, 25-hydroxyvitamin D.

<sup>2</sup> Median; range in parentheses (all such values).

<sup>3</sup> Mean ± SEM (all such values).

<sup>4</sup> Adjusted for age by ANOVA (PROC GLM; SAS Institute).

<sup>5</sup> Adjusted for age and energy intake by ANOVA (PROC GLM).

<sup>6–8</sup> Significantly different from quartile 1: <sup>6</sup> $P$  < 0.01, <sup>7</sup> $P$  < 0.0001, <sup>8</sup> $P$  < 0.05.

**TABLE 3**  
Association between body weight-adjusted AFM (kg) and TFM (kg) and BMD<sup>1</sup>

	Femoral neck BMD		Trochanter BMD		Total femur BMD		Lumbar spine BMD	
	$\beta$	95% CI	$\beta$	95% CI	$\beta$	95% CI	$\beta$	95% CI
Women ( <i>n</i> = 462) <sup>2</sup>								
AFM <sup>3</sup>	-0.056	(-0.080, -0.032)	-0.042	(-0.066, -0.018)	-0.047	(-0.074, -0.020)	-0.040	(-0.073, -0.008)
TFM <sup>3</sup>	-0.002	(-0.006, 0.001)	-0.006	(-0.010, -0.002)	-0.007	(-0.011, -0.003)	-0.004	(-0.009, 0.001)
Men ( <i>n</i> = 164)								
AFM <sup>3</sup>	-0.056	(-0.106, -0.006)	-0.048	(-0.096, 0.000)	-0.049	(-0.100, 0.003)	-0.011	(-0.075, 0.054)
TFM <sup>3</sup>	-0.008	(-0.015, -0.001)	-0.010	(-0.017, -0.004)	-0.010	(-0.017, -0.003)	-0.006	(-0.015, 0.003)

<sup>1</sup> Note that sample sizes for each analysis fluctuate around the reported value (approximate *n*) because of missing data for some covariates.  $\beta$ -Coefficients (and 95% CIs) were calculated by using ANCOVA (PROC GLM; SAS Institute). AFM, abdominal fat mass; BMD, bone mineral density; TFM, total fat mass.

<sup>2</sup> *n* = 463 for lumbar spine.

<sup>3</sup> Adjusted for age (y), current smoking status (yes or no), education (<9th grade, 9th–12th grade/General Education Development, some college/college or graduate school), alcohol intake (g/d), energy intake (kcal/d), season of BMD measurement (spring, summer, fall, or winter), osteoporosis prescription medication use (yes or no), physical activity score (%), calcium intake (mg/d), plasma 25-hydroxyvitamin D status (ng/mL), weight (kg), and height (m).

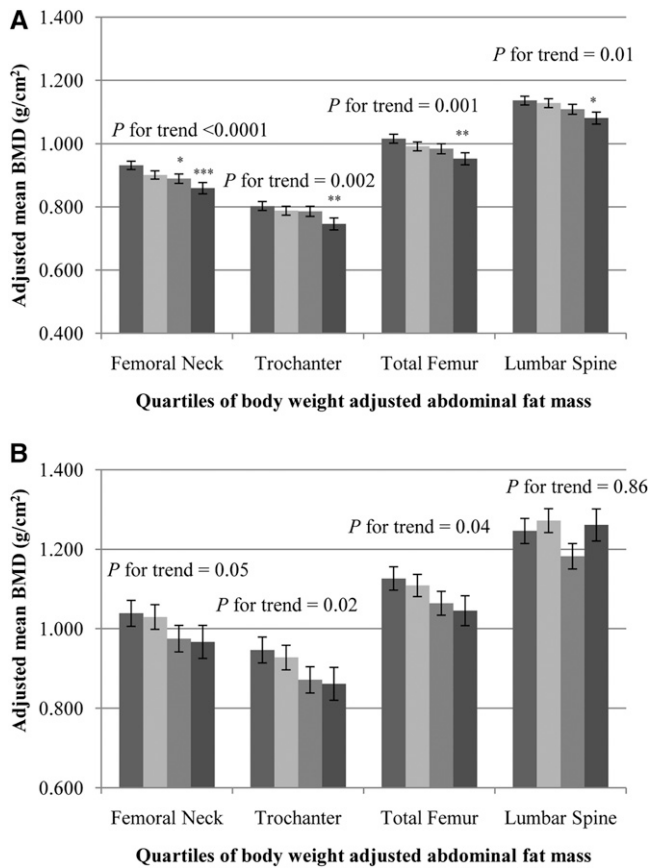
osteopenia at all 3 hip sites increased with every 100-g increase in body weight-adjusted AFM. Thus, AFM appears to have a strong inverse association with bone mass beyond the mechanical loading effect of body weight and differences in height. To our knowledge, the current study is the first to show the inverse association between AFM, measured by using DXA, and bone mass specifically in a Hispanic population.

The inverse associations between body weight-adjusted AFM and BMD are particularly noteworthy. Fat mass is a major component of body weight. Obesity, a condition characterized by excessive fat mass, has been traditionally thought to be protective for bone mass. In fact, low body weight, especially in older adults, is an established risk factor for osteoporosis. Moreover, in the WHO fracture risk assessment tool (23), a higher body weight is associated with a lower 10-y risk of fracture. The primary mechanism for the positive relation between fat and bone is due to the load on the skeleton by body weight. However, a few studies (24, 25) have shown that, when the mechanical loading effect of body weight is statistically removed, fat mass is negatively associated with bone. Most recently, Reid (26) contested that fat mass should not be adjusted for body weight because of the potential collinearity between the 2 variables. However, our hypothesis was that central fat mass is negatively associated with BMD after adjustment for the mechanical loading effect of body weight. To avoid collinearity between AFM and body weight, we included AFM residuals, as opposed to AFM, as our main exposure variable.

The differences in the effect sizes of body weight-adjusted AFM and TFM with BMD are particularly striking. AFM is known to be more metabolically and biologically active and produces a variety of autocrine and paracrine hormones, chemokines, and cytokines that affect bone metabolism. The flux of free fatty acids to the liver via the portal vein is greater in individuals with excess visceral fat. An increase in the delivery of free fatty acids to the liver signals a greater production of glucose output by the liver, which eventually leads to an insulin-resistant state (27). Insulin resistance, an essential feature of type 2 diabetes, has been shown to increase the risk of fracture (28, 29). A second potential mechanism for the negative association between body weight adjusted AFM and BMD may have to do with the

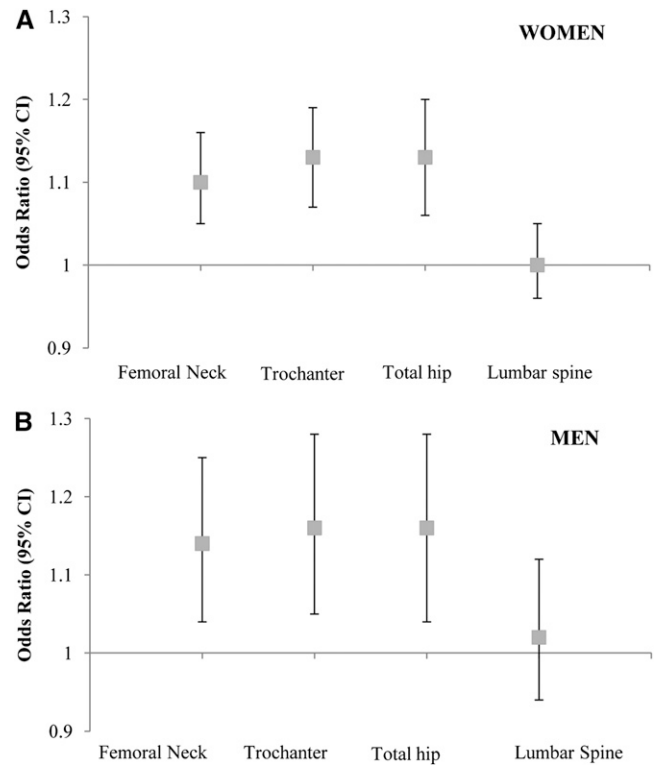
production of proinflammatory molecules such as IL-6 and TNF- $\alpha$ . Recent research has established that the release of many inflammatory adipokines by adipose tissue is enhanced in obese individuals, although these cytokines are primarily released by the nonfat cells of human adipose tissue (30). Visceral adipose tissue is known to release greater amounts of cytokines than is abdominal subcutaneous tissue (31). Concentrations of high-sensitivity C-reactive protein, a marker of systemic inflammation, are also elevated in individuals with abdominal obesity (32, 33), independent of BMI. Both prospective and cross-sectional analyses have indicated that higher circulating concentrations of proinflammatory cytokines—including C-reactive protein (34–36), IL-6 (37), and TNF- $\alpha$  (34)—are associated with lower BMD and greater fracture risk (38). In addition to a greater production of proinflammatory cytokines by abdominal adipose tissue, it is also known that production of adiponectin is reduced in obese individuals. Adiponectin, an adipose-derived hormone, is inversely associated with visceral fat (39, 40) and other measures of central obesity, such as waist circumference (41). Elegant in vitro and animal studies have elucidated the role of adiponectin on the skeleton. Adiponectin exerts an activity to increase bone mass by suppressing osteoclastogenesis and by activating osteoblastogenesis (42). Furthermore, the adiponectin receptors AdipoR1 and AdipoR2 are expressed in bone-forming cells (43). However, most recently, adiponectin knockout mice were shown to have increased bone mass, which suggests that adiponectin may have other indirect effects on bone (44). Finally, serum osteocalcin, a bone-derived protein that regulates bone formation, was recently found to be inversely associated with visceral adiposity (38). The modest effect sizes noted for associations of TFM and BMD may indicate that TFM may have small or negligible effects on BMD beyond its weight-bearing effect.

Our results are consistent with those from other studies that used computed tomography, magnetic resonance imaging, or anthropometric measure to determine abdominal obesity. Gilsanz et al (45) noted that visceral, but not subcutaneous, fat was negatively associated with the structure and strength of the femur in young women. Similarly, in a group of obese adolescent girls, visceral adipose tissue was a negative predictor of both hip and



**FIGURE 1.** Adjusted mean ( $\pm$ SEM) BMD by quartiles 1–4 (from left to right) of body weight–adjusted abdominal fat mass in women (A) and in men (B). Data were adjusted for age (y), current smoking status (yes or no), education (<9th grade, 9th–12th grade, General Education Development, some college, college, or graduate school), alcohol intake (g/d), energy intake (kcal/d), season of bone mineral density measurement (spring, summer, fall, or winter), osteoporosis prescription medication use (yes or no), physical activity score (%), calcium intake (mg/d), plasma 25-hydroxyvitamin D status (ng/mL), body weight (kg), and height (m) by using ANCOVA (PROC GLM; SAS Institute). Adjustment for multiple comparisons was performed by using Dunnett’s adjustment. A: quartile 1,  $n = 116$ , median (range) = 2.84 (1.84–3.06); quartile 2,  $n = 116$ , median (range) = 3.25 (3.07–3.38); quartile 3,  $n = 117$ , median (range) = 3.55 (3.39–3.67); quartile 4,  $n = 116$ , median (range) = 3.92 (3.68–5.09). \*\*\*\*Significantly different from quartile 1: \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ . B: quartile 1,  $n = 41$ , median (range) = 2.38 (1.63–2.68); quartile 2,  $n = 41$ , median (range) = 2.86 (2.69–3.05); quartile 3,  $n = 41$ , median (range) = 3.27 (3.06–3.45); quartile 4,  $n = 41$ , median (range) = 3.64 (3.46–4.96). BMD, bone mineral density.

spine BMD (46). Likewise, Huang et al (47) showed that lumbar spine BMD is reduced in association with greater visceral fat in HIV-infected men with lipodystrophy. Using waist-to-hip ratio as a marker for visceral fat, 2 independent studies in Korean men (48) and postmenopausal women (49) found that BMD of the calcaneus (48) and the lumbar spine (49) were negatively correlated with waist-to-hip ratio, after adjustment for BMI or body weight. Unlike the study populations of Huang et al (47), Russell et al (46), and Kim et al (49), we found no associations at the lumbar spine in men, possibly because of the presence of osteophytes, disc space narrowing, and end-plate sclerosis and the presence of other structural artifacts such as extraskelatal calcifications. Lumbar spine BMD measurements can be confounded by these structural artifacts that can artificially increase



**FIGURE 2.** ORs (and 95% CIs) of osteoporosis or osteopenia for every 100-g increase in body weight–adjusted abdominal fat mass in women ( $n = 465$ ; A) and in men ( $n = 164$ ; B). Adjusted for age (y), current smoking status (yes or no), education (<9th grade, 9th–12th grade, General Education Development, some college, college, or graduate school), alcohol intake (g/d), energy intake (kcal/d), season of bone mineral density measurement (spring, summer, fall, or winter), osteoporosis prescription medication use (yes or no), physical activity score (%), calcium intake (mg/d), plasma 25-hydroxyvitamin D status (ng/mL), body weight (kg), and height (m) by using logistic regression (PROC LOGISTIC; SAS Institute).

the BMD measurement (50, 51). Nevertheless, our finding of a strong association of AFM with femoral neck BMD is of public health importance because the death rate within 1 y of a fractured neck of femur is between 20% and 35% (52).

The results of the current study should be interpreted in the context of a few limitations. First, because we used DXA to measure AFM, we were unable to differentiate between visceral and subcutaneous fat. In addition, we had no data to validate AFM against measures of visceral fat from computed tomography or magnetic resonance imaging. However, a recent study in adolescent girls showed that percentage trunk fat from DXA was more significantly associated with visceral ( $r = 0.83$ ,  $P < 0.0001$ ) than with subcutaneous ( $r = 0.77$ ,  $P < 0.0001$ ) fat (53). Furthermore, whereas visceral fat is thought to be more strongly associated with disease risk, a recent study showed that measures of central obesity were better associated with coronary artery calcium than with direct measures of visceral adiposity (54). These data suggest that the total amount of central obesity is more important than the relative distribution of visceral compared with subcutaneous fat. Still, future studies should evaluate the independent roles of visceral compared with subcutaneous fat depots on bone. Second, as with any observational study, residual confounding is still a possibility. However, covariates included in our models were carefully selected on the

basis of underlying biological mechanisms. Finally, our study was cross-sectional in nature; hence, we were unable to make inferences of causality.

In conclusion, our finding of a negative association between AFM and bone mass in a Hispanic population provides compelling evidence that AFM is a significant risk factor for osteoporosis. Although our results should be replicated in other populations, our findings support the urgent need for development of public health programs tailored to specific ethnic groups that focus on the prevention and treatment of abdominal obesity.

The authors' responsibilities were as follows—SNB and KLT: study design; SNB: data analysis, data interpretation, and manuscript writing; KLT: study oversight; and BD-H, MTH, and AHL: data interpretation and critical revision of the manuscript. The authors had no conflicts of interest.

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