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**Clinical Research Article**

# Fat Mass Has Negative Effects on Bone, Especially in Men: A Cross-sectional Analysis of NHANES 2011-2018

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## Abstract

**Context:** The effect of high levels of obesity on bone health are not clear.

**Objective:** We aimed to examine the associations of body composition and bone mineral density (BMD) in a large, nationally representative population with a wide range of body mass index.

**Methods:** We analyzed 10 814 subjects aged 20-59 from NHANES 2011-2018 who had total body BMD and body composition data. Body composition was examined as lean mass index (LMI) and fat mass index (FMI). Linear regression models were created with BMD as the outcome, while examining LMI and FMI and controlling for age, gender, race/ethnicity, height, and smoking status.

**Results:** In multivariable modeling, every 1 kg/m$^2$ additional LMI was associated with 0.19 higher T-score, while every additional 1 kg/m$^2$ in FMI was associated with 0.10 lower T-score ($P < .001$ for both). The negative association of FMI with BMD was mainly seen when adjusting for LMI. Effects of LMI were similar in men and women, but the effect of FMI was more negative in men (0.13 lower T-score per additional 1 kg/m$^2$ of FMI in men vs 0.08 lower BMD T-score in women, $P$ for interaction < .001).

**Conclusion:** In subjects under 60 years old, lean mass had a strong positive association with BMD. Conversely, fat mass had a moderate, negative association with BMD that was most notable in men at high levels of fat. Our results emphasize the importance of bone health in obesity and may explain site-specific increases in fracture rates in some studies of obese subjects.

**Key Words:** body composition, obesity, bone density, gender differences, osteoporosis

**Abbreviations:** bioE2, bioavailable estradiol; bioT, bioavailable testosterone; BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; FMI, fat mass index; LMI, lean mass index; SHBG, sex hormone–binding globulin; TB, total body.

Studies have demonstrated a strong positive relationship between body weight and bone mineral density (BMD) (1). However, this relationship has been less well studied in the context of the current obesity epidemic, where very high levels of obesity have become commonplace. In fact, the level of severe obesity (defined as BMI ≥ 40 kg/m$^2$) has more than tripled from 2.8% of the population in 1988-1994 to 9.3% in 2017-2018 (2, 3). In general, increasing BMI in women has been associated with lower fracture risk at most sites (4). However, obesity is associated with higher risk of fracture at the humerus (4, 5), and a few studies report higher risk at other sites as well (6, 7). Moreover, studies in men are scarcer and conflicting (8-11).

These studies challenge conventional thinking and require a re-examination of our understanding of how weight may affect BMD. In particular, the makeup of body weight, or body composition, may impact how weight and BMD are related. Body composition measurement separates the components of weight into lean mass, fat mass, and bone mass. Previous work has suggested that lean mass has a strongly positive influence on bone mass, while the effects of fat mass are less clear (12-17). In general, this work has been limited by the fact that body composition is not a routine clinical measurement. Most studies, therefore, have been limited by small numbers, referral bias (eg, recruiting from an osteoporosis population), lack of racial or ethnic diversity, and/or use of estimated, rather than measured, body composition.

The National Health and Nutrition Examination Survey (NHANES) recently released total body (TB) dual-energy x-ray absorptiometry (DXA) data from years 2011-2018, encompassing over 10 000 subjects of diverse backgrounds and a large range of weight and body composition. While traditional bone density measurements of the hip and spine are not available in all years, we have recently demonstrated that TB DXA measures, such as TB BMD, are strongly correlated with regional hip and spine BMD and are associated with prior fractures similarly to regional scans (18). Therefore, we used NHANES 2011-2018 data to study the associations of body composition with TB BMD in a wide range of BMI including those with severe obesity.

## Materials and Methods

### Subjects

Subjects who underwent TB DXA in NHANES 2011-2018 were studied. Methods used in NHANES have been reported previously (19). Briefly, NHANES is a nationally representative US sample that uses a complex survey design. NHANES administers questionnaires, conducts laboratory and exam testing, and collects demographics data, such as age, gender

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(determined by NHANES staff or reported by the subject), and self-reported race/ethnicity.

### BMD Measurements

A subset of subjects aged 8-59 underwent TB DXA with Hologic Discovery model A densitometers (Hologic, Inc., Bedford, MA). Pregnant women and those with weight over 450 LB, height over 6 ft 5 in (1.96 m), or those with use of radiographic contrast material within the past 7 days were excluded. The University of California San Francisco reviewed all scans for accuracy and consistency. The main reasons for completed but invalid scans were an insufficient scan area or partial scan. In our analysis, we restricted the subjects to those with valid data over age 20 (ie, 20-59). For our sensitivity analysis, we also examined associations between body composition and regional hip and spine examinations. These had been done in years 2013-2014 (n = 1408) and years 2017-2018 (n = 478) using Hologic QDR-4500A fan-beam densitometers (Hologic, Inc., Bedford, MA). Because they were not done in adjacent cycles, the subjects could not be combined due to the weights being unreliable, and year 2013-2014 was used as the subpopulation of interest given its larger sample size.

For BMD measurements, we focused on TB BMD. We chose this site based on our prior work showing high correlation to regional DXA (TB: $r$ = 0.73, 0.73, 0.71 for dedicated lumbar spine, total hip, and femoral neck, respectively) and similar associations with prior fracture as regional sites (18). We calculated T-scores for these sites from reference data. Reference populations of Caucasian females aged 20-29 from NHANES 2011-2018 were used (n = 463). For our sensitivity analysis using regional hip and spine BMD from NHANES 2013-2014, we calculated T-scores using NHANES 2005-2008 (n = 236-262) since regional hip and spine examinations were not available in all years 2011-2018. The same densitometer (Hologic QDR 4500A) was used for regional hip and spine measurements in NHANES 2005-2008 as in NHANES 2013-2014.

### Body Mass Index, Body Composition, and Sex Hormones

For weight and body mass index (BMI) in Table 1, we used weight and BMI as provided by NHANES; however, for 4 subjects who had TB composition but no recorded weight, we imputed weight as the sum of total lean mass, fat mass, and bone mass and calculated BMI as weight divided by height squared. For examining the effects of body composition on TB BMD, lean mass index (LMI) and fat mass index (FMI) were generated. LMI is lean mass divided by height squared, while FMI is fat mass divided by height squared. For examining the relationship between TB BMD and LMI and FMI, subjects were stratified into sex-specific quartiles. The exact cutoff for each quartile is provided in an online repository (20). For the purposes of this analysis, all references to lean mass excludes bone mass. We also examined separately the effect of appendicular and trunk soft tissue measurements. Appendicular lean and fat mass are the sum of both arms and legs lean or fat mass, respectively. We normalized these measures for body size by dividing by height squared.

Testosterone, estradiol, sex hormone–binding globulin (SHBG), and albumin levels were examined in a subgroup of subjects who had these measurements available in NHANES 2013-2016 (46.4% of men and 47.5% of women). Testosterone and estradiol were performed in NHANES via isotope dilution liquid chromatography tandem mass spectrometry based on the National Institute for Standards and Technology's reference method. SHBG measurement is based on the reaction of SHBG with immune antibodies and chemoluminescence. In our analysis, we calculated bioavailable testosterone (bioT) and bioavailable estradiol (bioE2) based on the methods of Södergard and described by De Ronde (21, 22). Only testosterone measurements from NHANES 2013-2016 were used, as SHBG was not available in NHANES 2011-2012 for bioavailable hormone calculations. Menopause status (available in 92.5% of women) was also examined and considered present if women reported they had not had a period in 12 months.

### Statistical Analysis

All analyses were conducted with Stata 16 (StataCorp, College Station, TX) and were done using population-based sampling weights to account for the complex survey design of NHANES. Standard errors of the mean for all estimates were obtained using a linearization method (Taylor series). In subpopulation analyses, strata with a single sampling unit were centered at the overall mean to calculate standard errors. Adjusted Wald tests were used to compare demographic variables and bone density at each site. Linear regression models were created with BMD as the outcome, while examining LMI and FMI and controlling for age, gender, race/ethnicity, height, and smoking status. In general, age was examined in 5-year age groups to properly model differences in how age affects BMD, particularly in those over 50. However, for simplicity of results, age was analyzed by decade when examining interactions with body composition and TB BMD. "Other" race was not analyzed separately due to likely heterogeneity of this group. BMI was not included in regression models due to strong collinearities with LMI/FMI (variance inflation factors >100). Strongly collinearity was not present between LMI, FMI, and height (variance inflation factors <2).

To compare the importance of lean and fat mass distribution (trunk vs appendicular), we used linear regression using BMD as the outcome variable and a lean mass variable and a fat mass variable as predictors, while adjusting for age, gender, race/ethnicity, smoking status, and height. Standardized coefficients (β) were used to compare between lean mass or fat mass measures, and $R^2$ was used to compare the models.

## Results

### Subjects

The subjects' characteristics are presented in Table 1, stratified by BMI. The nonobese group (BMI < 30 kg/m$^2$) was younger and less ethnically diverse than the obese (BMI 30-40 kg/m$^2$) and severely obese (BMI ≥ 40 kg/m$^2$) groups. They also had lower TB BMD than the obese and severely obese group. In the severely obese group, there were significantly fewer men than the other 2 groups. Lean mass and fat mass were significantly different overall, but there was a notable amount of overlap between BMI categories.

### Associations Between BMD and BMI or Body Composition

In univariate analyses, TB BMD was significantly associated with BMI and LMI (0.025 higher T-score and 0.14 higher

**Table 1.** Demographics, body composition, and BMD by BMI strata

| | BMI < 30 (6795) | BMI 30-40 (3248) | BMI ≥ 40 (771) |
|---|---|---|---|
| Age | 38.7 ± 9.8* | 40.8 ± 9.3 | 40.4 ± 9.7 |
| BMI | 24.8 ± 2.6* | 33.7 ± 2.2* | 44.8 ± 3.8* |
| Male | 51.4% | 51.5% | 33.6%* |
| Race | 63.0% White* | 58.3% White | 58.6% White |
| | 9.5% Black* | 13.0% Black* | 18.6% Black* |
| | 8.7% MA* | 13.6% MA | 12.2% MA |
| | 7.2% HIS | 8.4% HIS* | 6.2% HIS |
| | 8.3% Asian* | 2.7% Asian* | 0.6% Asian* |
| | 3.3% Others | 4.0% Other | 3.7% Other |
| Height (cm) | 169.3 ± 7.7* | 168.5 ± 7.9* | 167.1 ± 7.7* |
| Currently smoking | 22.1% | 21.0% | 20.4% |
| Total body BMD (gm/cm$^2$) | 1.105 ± 0.086* | 1.128 ± 0.089 | 1.130 ± 0.088 |
| Lean mass (kg) | 48.1 ± 8.5* | 58.7 ± 9.6* | 68.1 ± 11.1* |
| Lean mass index (range) (kg/m$^2$) | 16.6 ± 1.9* (8.6-24.0) | 20.4 ± 1.9* (14.2-28.7) | 24.2 ± 2.4* (18.6-35.1) |
| Fat mass (kg) | 21.4 ± 5.1* | 35.2 ± 5.7* | 54.9 ± 8.0* |
| Fat mass index (range) (kg/m$^2$) | 7.6 ± 1.9* (2.1-14.3) | 12.5 ± 2.3* (5.5-20.1) | 19.8 ± 3.1* (10.1-35.4) |

Mean ± SD. Astericks (*) are significantly different from the other 2 BMI groups.
Abbreviations: BMI, body mass index. BMD, bone mineral density. MA, Mexican Americans. HIS, Hispanic of other origin.

**Table 2.** Regression coefficients of LMI, FMI, and BMI per 1 kg/m$^2$ on total body BMD T-score when minimally, partially, or fully adjusted

| | Minimally adjusted | Partially adjusted | Fully adjusted (including both LMI and FMI) |
|---|---|---|---|
| LMI | 0.10 (0.09-0.11) | 0.09 (0.08-0.10) | 0.19 (0.18-0.21) |
| FMI | 0.017 (0.010-0.025) | 0.016 (0.008-0.023) | –0.10 (–0.11 to –0.08) |
| BMI | 0.028 (0.024-0.032) | 0.026 (0.021-0.030) | — |

95% CI in parenthesis. All values statistically significant ($P < .001$). Minimal adjustment includes only age and sex. Partial adjustment includes age, sex, race, height, and smoking status. Full adjustment includes all of the variables in partial adjustment, as well as both LMI and FMI simultaneously included. Body composition and BMI were not included in the same model due to excess collinearity (see "Materials and Methods").

T-score per 1 kg/m$^2$ increase, respectively, $P < .001$ for both). In univariate analysis, TB BMD had a slight negative association with FMI (0.025 lower T-score per 1 kg/m$^2$ increase, $P < .001$), though the association was weak and became slightly positive with age and sex adjustment (Table 2). Most notably, the associations for LMI and FMI were substantially impacted by adjusting for one another. When including both LMI and FMI in the same model, each 1 kg/m$^2$ of LMI was associated with 0.19 higher T-score, and each 1 kg/m$^2$ of FMI was associated with 0.09 lower T-score ($P < .001$ for both). The associations of LMI and FMI to TB BMD are shown graphically in Fig. 1, where mean TB BMD is shown at each quartile of LMI and FMI without adjustment ($P$ for trend for LMI across each FMI quartile <.05, $P$ for trend for FMI across each LMI quartile <.05 except LMI quartile 1 where $P$ = NS). TB BMD T-scores stratified by World Health Organization BMI categories are also provided in an online repository (20).

## Multivariable Modeling

In multivariable modeling that included age, gender, race/ethnicity, height, smoking status, LMI, and FMI, the associations of LMI and FMI to TB BMD largely persisted (Table 2). As above, we found a stronger positive effect of LMI on TB BMD than negative effect of FMI. Every 1 kg/m$^2$ additional LMI was associated with 0.19 higher T-score, while every additional 1 kg/m$^2$ in FMI was associated with 0.10 lower T-score ($P < .001$ for both). This is depicted graphically in Fig. 2. As seen in Table 2, the magnitude of associations was affected by covariate adjustments. In particular, the magnitude of association for LMI became substantially more positive and the association for FMI substantially more negative when adjusting for one another. Other covariate adjustments had relatively less impact on the association of LMI or FMI to TB BMD. There was no evidence for nonlinearities in the relationship of FMI or LMI with TB BMD based on plotting of the residuals of the model against FMI or LMI, respectively. Results were similar when excluding height as a covariate.

## Differences by Gender, Age, Race/Ethnicity, or BMI Strata

When examining men and women separately, the negative effect of FMI was stronger in men than women. In multivariable modeling, every additional 1 kg/m$^2$ of FMI was, on average, associated with 0.08 lower BMD T-score in women, but 0.13 lower BMD T-score in men ($P$ for interaction <.001). The effect was most prominent in the highest quartile (Fig. 3). There was no interaction between gender and LMI. We also examined if there were differences in premenopausal (67.3% of women with menopausal status available) vs postmenopausal

women—while postmenopausal women had lower BMD T-score (–0.37 vs 0.23 BMD T-score, $P < .001$), there was no interaction of menopausal status with LMI or FMI on BMD.

We examined the effects of age on the relationship between body composition and BMD. There were slightly stronger relationships between LMI and TB BMD in the age 20-29 and age 50-59 groups compared with the other subjects (Fig. 4, $P$ for interaction by age = .01). However, the relationship between FMI and TB BMD did not differ between age groups.

By race/ethnicity, only Mexican Americans showed a slightly less positive effect of LMI than White people (0.16 T-score per 1 kg/m$^2$ vs 0.21 T-score, $P$ for interaction = .004). There were no other interactions between race/ethnicity and LMI or FMI. We also examined BMI strata (BMI < 30 kg/m$^2$ vs 30-39.9 kg/m$^2$ vs ≥40 kg/m$^2$, n = 6795, 3248, and 772, respectively). The effect of LMI on TB BMD was attenuated with increasing strata (0.24 T-score vs 0.17 T-score vs 0.11 T-score per 1 kg/m$^2$ for BMI < 30, BMI 30-39.9, and BMI ≥ 40 kg/m$^2$, $P$ for interaction < .001 for higher strata vs lowest strata). The effect of FMI did not significantly differ by BMI strata when accounting for the change in LMI with BMI.

## Sensitivity Analysis using Regional DXA

We examined total hip, femoral neck, and spine BMD from 1408 subjects and compared with TB BMD. In these subjects, LMI had a similar effect at the regional sites as TB BMD T-score (eg, FN T-score 0.22 T-score increase per 1 kg/m$^2$ vs TB T-score 0.24 T-score increase per 1 kg/m$^2$, $P$ = NS). However, the effect of FMI was attenuated at the regional sites and only present in men, while in women there was no effect of FMI at the regional sites (Table 3). There was a significant negative relationship between FMI and TB BMD in these subjects, however.

## Relationship Between BMD and Sex Hormones

Given gender differences in the association of BMD and fat mass, we further examined how bioT and bioE2 levels varied by FMI in men and women. Mean bioT and bioE2 levels were 257 ng/dL and 18.4 pg/mL in men, and 10.6 ng/dL and 42.9 pg/mL in women, respectively. In men, bioT was negatively correlated with FMI (r = –0.35, $P < .001$) while bioE2 was positively correlated with FMI (r = 0.23, $P < .001$). TB BMD was only positively correlated with bioE2 in men (r = 0.15, $P < .001$). In women, bioE2 was not correlated with FMI, while bioT was (r = 0.10 $P < .01$). Like in men, TB BMD was only correlated with bioE2 in women (r = 0.16, $P < .001$). Multivariable regression models with TB BMD as the outcome confirmed bioE2, not bioT, as a significant predictor of BMD in men and women. Among a subsample with regional hip and spine BMD, results were generally similar for total hip, femoral neck, and spine BMD in men (n = 606). In women (n = 615), bioE2 and bioT were both significantly correlated with total hip T-score (r = 0.26 and 0.13, respectively, $P < .001$ and $P = .02$) but in multivariable regression, again, only bioE2 was significantly correlated with total hip T-score.

## Effect of Regional Compared With Total Lean or Fat Mass

We compared the effect of regional (ie, trunk vs appendicular) soft tissue to the effect of total soft tissue on BMD. In general, the various lean mass measures were highly correlated ($r$ = 0.87-0.97), as were the various fat mass measures ($r$ = 0.86-0.97). In fully adjusted regression models, standardized coefficients for lean and fat mass measures were generally similar regardless of what region was analyzed, and overall models performed similarly (Table 4). This was the case when examining by region together (eg, lean and fat mass from the

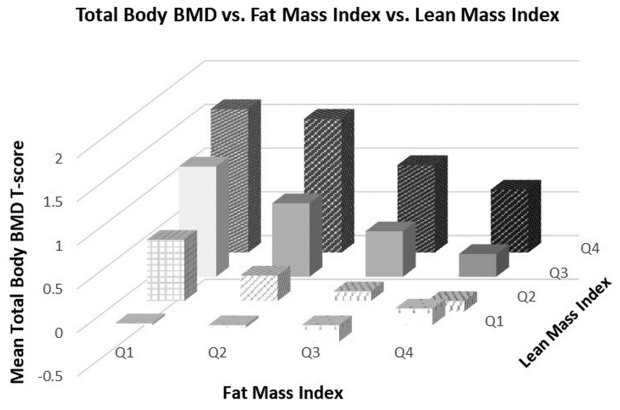


**Figure 1.** Mean total body BMD T-score by lean mass and fat mass quartile. See text for further details.

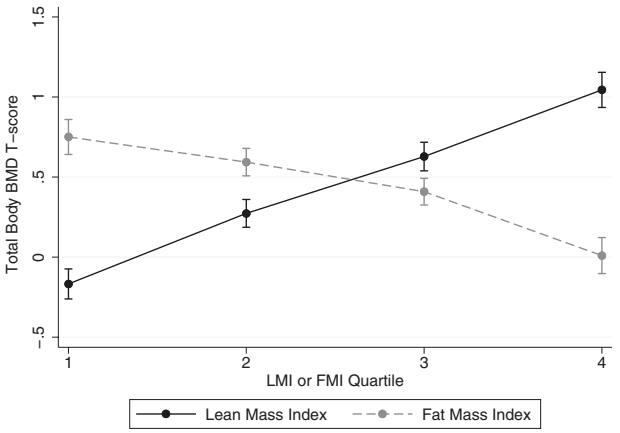


**Figure 2.** Total body BMD T-scores by LMI or FMI quartile, as predicted by a model that adjusts for age, gender, race/ethnicity, smoking status, height, and FMI or LMI, respectively.

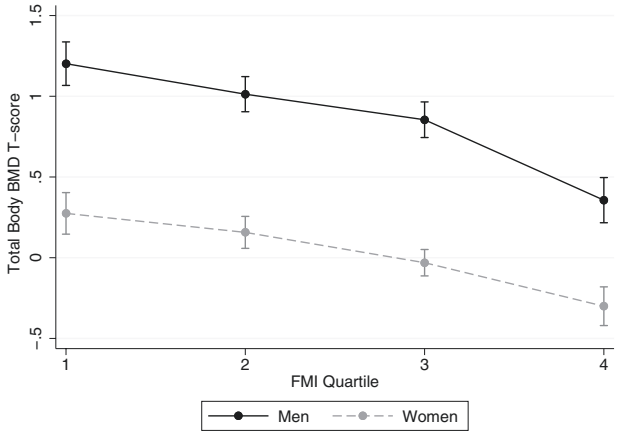


**Figure 3.** Total body BMD T-scores by gender and FMI quartile, as predicted by a model that adjusts for age, race/ethnicity, smoking status, height, and LMI.

trunk) or when mixing regions of lean and fat mass measures (eg, trunk fat and appendicular lean mass). Appendicular fat mass had somewhat weaker associations with BMD than trunk fat, including in combination with total lean mass (data not shown). Conclusions were generally similar in men and women, though there were stronger negative effects of fat in men regardless of region.

## Discussion

In a large, diverse population with a wide range of BMI, we found clear evidence that bone density is negatively associated with fat mass and positively associated with lean mass. While lean mass had an overall stronger effect than fat, the negative effects of fat on BMD were particularly pronounced in men and in those with the highest levels of fat. These findings suggest that obesity could lead to declines in BMD in patients who are not typically considered at high risk for fracture and may not undergo DXA screening. Our results, which also show differences by BMD site, may also help explain the differences in site-specific fracture risk seen in large obesity studies (5, 7). Unlike prior work which has been limited by referral bias and/or small numbers, our findings reflect the general US population and suggest that obesity alone does not guarantee against low BMD and should not dissuade clinicians from assessing bone density, particularly if other risk factors are present.

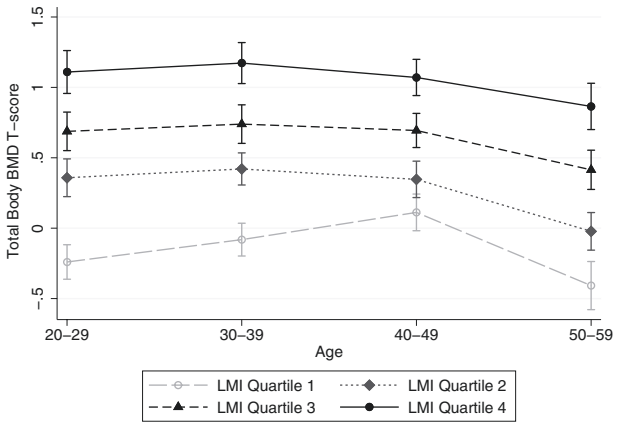


**Figure 4.** Total body BMD T-scores by age and LMI quartile, as predicted by a model that adjusts for gender, race/ethnicity, smoking status, height, and FMI.

Our results confirm the previously reported positive association between lean mass and BMD (12, 14). However, prior studies have found inconsistent effects of fat mass including positive, neutral, or slightly negative (12-14, 16, 17). In contrast, we found more prominent negative effects of fat mass, particularly at high levels of fat. Our study may differ from some previous studies in that we normalized soft tissue by body size (ie, LMI and FMI) and studied a US representative racially and ethnically diverse population which included significant numbers of men. Furthermore, previous studies, some of which are 15-20 years old, may not reflect current trends in severe obesity, which has been increasing substantially in the United States and projected to worsen (23). The densitometer used in the study, the Hologic Discovery, also has a higher weight limit (450 lb. [204 kg]) than many previous densitometers and may have allowed for examination of higher levels of obesity than previously studied.

Additionally, analytic factors may play a role in differences seen in the association between bone density and body composition across studies. When examining the separate effects of lean mass and fat mass, it is important to recognize that both measures are correlated with one another and with body weight or BMI. Excessive collinearity can result if variables have high correlation and requires careful inspection of analytic models to avoid—this is a particular concern if body composition and body weight or BMI are entered into the same model (24). On the other hand, if one examines fat mass without consideration of lean mass, the effect of lean mass (the omitted variable) will bias the estimate for fat mass due to the correlation of FMI and LMI, a statistical concept known as omitted variable bias (25). In our study, we observed FMI generally had a slight association with BMD (negative or positive, depending on the adjustment) when LMI was not considered; this is likely due to the correlation between FMI and LMI, rather than the true effect of FMI. When LMI was properly introduced into the model, FMI had a moderately negative association with BMD.

FMI had a stronger negative effect on bone density in men than women, and we only observed negative effects of FMI at regional BMD sites in men. Several studies have specifically examined gender differences in the associations of body composition and bone density. While some studies have reported positive effects of fat mass on BMD in women, but no effect

**Table 3.** Regression coefficients for the effect of FMI on total body, femoral neck, total hip, and spine T-scores by FMI quartile among 1408 subjects, adjusted for age, race/ethnicity, LMI, smoking status, and height

| | | FMI quartile | | | | |
|---|---|---|---|---|---|---|
| | BMD T-score | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | *P* value (trend) |
| Women | TB | Reference | –0.01 | –0.38 | –0.33 | .04 |
| | FN | Reference | 0.18 | 0.03 | 0.08 | .90 |
| | TH | Reference | 0.33 | 0.24 | 0.24 | .32 |
| | Spine | Reference | 0.21 | 0.13 | 0.22 | .54 |
| Men | TB | Reference | 0.05 | –0.38 | –0.90 | <.001 |
| | FN | Reference | –0.03 | –0.25 | –0.47 | <.001 |
| | TH | Reference | 0.06 | –0.03 | –0.28 | .002 |
| | Spine | Reference | 0.13 | –0.12 | –0.40 | .049 |

Abbreviations: FN, femoral neck; TB, total body; TH, total hip.

**Table 4.** Standardized coefficients (β) by lean or fat mass region, ie, the change in Total Body T-scores per 1 SD increase in lean or fat mass, adjusted for age, gender, race/ethnicity, smoking status, and height

| Lean region analyzed | β, lean mass (95% CI) | Fat region analyzed | β, fat mass (95% CI) | $R^2$(model) |
|---|---|---|---|---|
| Trunk lean | 0.65 (0.59-0.71) | Trunk fat | –0.45 (–0.51 to –0.38) | 0.30 |
| Appendicular lean | 0.57 (0.51-0.63) | Appendicular fat | –0.30 (–0.35 to –0.24) | 0.29 |
| Total lean | 0.66 (0.60-0.72) | Total fat | –0.43 (–0.50 to –0.37) | 0.30 |
| Total lean | 0.69 (0.63-0.75) | Trunk fat | –0.42 (–0.49 to –0.36) | 0.31 |
| Appendicular lean | 0.61 (0.55–0.68) | Total Fat | –0.32 (–0.38 to –0.26) | 0.30 |
| Appendicular lean | 0.61 (0.54-0.67) | Trunk Fat | –0.29 (–0.34 to –0.23) | 0.30 |

Abbreviations: β, standardized coefficient; CI, confidence interval.

in men (26, 27), other studies have reported similar effects in men and in women (9, 28). Fat mass may have different effects in men and women, and we demonstrated that testosterone in men had much stronger negative relationships with fat mass than estradiol in women. However, like prior work, we found that bioE2, not testosterone, was an important predictor of BMD (29, 30), suggesting sex hormones alone do not explain gender differences in the interaction between BMD and fat and that more complex mechanisms are at play. While women have higher percentages of body fat than men, studies demonstrate that women tend to accumulate fat in the hip and thighs, while men accumulate fat in the trunk and abdomen (31). Though we did not find conclusive evidence that fat distribution affects BMD, we cannot rule out that differences in abdominal visceral fat or other body distribution factors not analyzable in our study could play a role in gender differences in the effect of fat mass on BMD.

Along with gender differences, we also found that fat mass had a moderately negative association with TB BMD, but the association was weaker for regional hip and spine BMD. The differences between BMD sites in our study mirrors other studies that report weaker positive associations of fat mass with TB BMD than other BMD sites (13, 15), though this is not a uniform finding (26). It is possible that this finding, too, is related to hormonal effects, and we found that bioT was correlated with FMI and total hip BMD, but not TB BMD, in women. It has also been demonstrated that estrogen therapy can affect BMD sites differently—in the Women's Health Initiative, estrogen therapy led to greater increases in BMD at the hip and spine than the TB (32). However, the mechanism of the effect of fat mass on BMD may not be limited to sex hormones and has been hypothesized to involve leptin, insulin, adiponectin, etc. (33, 34). Therefore, it is possible that 1 or more of the hormonal changes in obesity could have different effects throughout the skeleton. It should be noted that even though fat mass associations with regional sites were weaker than for TB BMD, prior studies, including our own, have indicated that TB DXA regions are similarly associated with fracture risk as regional BMD sites (18, 35). Therefore, lower TB BMD related to fat mass could suggest increased fracture risk, even in women.

In general, we found lean mass had stronger associations with TB BMD than fat mass and that the association of LMI with TB BMD did not appear to plateau, even at high levels of lean mass. This is notable given the range of lean mass among the subjects. We did, however, find weaker positive effects of LMI in Mexican Americans. Unfortunately, Mexican Americans have high rates of obesity and, therefore, could be more likely to experience these negative bone health effects (36). The mechanism of a reduced effect of LMI on BMD in Mexican Americans is uncertain, though similar findings have been reported previously (37, 38). Because muscle mass is not the same as muscle strength, it is possible that the same muscle mass may be associated with different levels of strength in different ethnicities, thus differentially affecting BMD (39).

We also examined if trunk or appendicular soft tissue measures were stronger predictors than total soft tissue. Overall, we found that total LMI and FMI were not significantly different predictors than appendicular or trunk soft tissue measures for TB BMD. This may suggest that it is unnecessary to consider appendicular lean mass specifically (as opposed to total lean mass) in defining sarcopenia or evaluating abdominal fat specifically (as opposed to total fat mass) for bone outcomes. However, we did not examine abdominal visceral fat, which has been shown to be potentially more deleterious to bone than subcutaneous abdominal fat (40). Abdominal visceral fat, which can be measured by DXA, is more metabolically active than subcutaneous abdominal fat, and its impact on bone health deserves further study.

Our study has several important strengths. Because TB DXA is primarily a research tool, very few studies of TB DXA are of the size of our study. This allowed for more power to see differences between groups when present. Furthermore, NHANES uses a complex, multistage probability sampling design to represent the US population as a whole. This means that, in comparison with other body composition studies, our study population is much more diverse. Indeed, very few studies include so many men or racial and ethnic minorities to allow for comparison. Similarly, the design of NHANES means our study was not subject to referral bias, as could be the case in studies recruiting from physician clinics or from subjects undergoing regional DXA for osteoporosis screening. Finally, because of obesity trends in the United States, there were wide ranges of lean mass and fat mass in the study, allowing for a comprehensive investigation of the associations between bone density and body composition.

Some limitations should be noted. Studies have demonstrated that BMD (both TB and regional BMD) at high levels of fat may be affected by soft tissue artifacts and could be unreliable (41-43). However, importantly, the direction of error is unpredictable. Therefore, we do not believe our findings, particularly low BMD at high levels of fat, are explained by soft tissue interference. Second, as already mentioned, we used TB DXA regions, rather than regional scans, due to availability. While regional scans are traditionally associated with fracture risk, studies have indicated that TB DXA is similarly associated with fractures as regional hip and spine BMD. Third, our subjects were limited to those under age 60,

and we acknowledge some studies have found differences in the relationship of body composition and bone mass in older subjects compared with younger subjects (28, 44, 45). Finally, NHANES does not conduct hip structural analysis and, therefore, we could not examine the effect of body composition on these parameters. Many investigators have found relationships between soft tissue indices and hip indices, which may be an important aspect of fracture risk in obese subjects (12, 14).

In conclusion, in a large US representative population of over 10 000 subjects, we found fat mass was negatively correlated with bone density, particularly in men at high levels of fat. We also found strong positive relationships between lean mass and bone density even at high levels of lean mass. Our results emphasize the importance of bone health as obesity trends worsen in the United States and may explain higher rates of fracture at certain sites in at least some studies of obese subjects (4-7). Further work is necessary to understand the effects of high fat mass on the risk of fracture, devise appropriate osteoporosis screening strategies in obese patients, and determine whether negative effects of fat on bone mass are reversible with weight loss.

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## Disclosure Summary

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## Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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