A multicenter study of the influence of fat and lean mass on bone mineral content: evidence for differences in their relative influence at major fracture sites


ABSTRACT We examined the relative influence of fat and lean mass on bone mineral content (BMC) among 1600 early postmenopausal women aged 45–59 y from four geographical locations (Nottingham, United Kingdom; Portland, OR; Honolulu; and Copenhagen). Bone sites investigated included the major fracture sites: hip, spine, and radius. Body weight had strong associations at all skeletal sites examined [BMC differences of 4–6% per interquartile range (IQR) of weight]. Associations with the fat and lean components of weight were more variable. The BMC differences per IQR of lean mass were 5–7% at the hip sites, 3% at the spine, and 2% at the radial sites. The greater differences for lean mass at the hip may reflect the high physical mobility and muscular activity of this site. The BMC differences per IQR of fat mass were 4–6% at the hip sites, 4% at the spine, and 5% at the ultradistal radius. These results suggest that low fat mass or low lean mass, particularly at the extremes, may adversely affect the major fracture sites. The bone sites with the greatest differences for fat mass were the most highly trabecular sites. With only a few exceptions, the associations of BMC with fat mass and lean mass were similar in direction and comparable in magnitude across the four geographic locations. We conclude that both fat and lean mass have independent influences on bone mass, but that their relative influence may vary by bone site depending on the trabecular content, physical mobility, and muscularity of the site. Am J Clin Nutr 1996;64:354–60.

KEY WORDS Body composition, bone mineral content, fat mass, lean mass, menopause, multicenter study

INTRODUCTION

It is well established that body weight is positively associated with bone mass (1–4). Few studies, however, have examined the relative importance of the fat and lean components of body weight for skeletal mass—and the findings are contradictory. Some authors have reported that fat mass most strongly predicted bone mass; other authors have concluded that lean mass was the stronger predictor (5–8). In some studies, both fat and lean body mass were associated with bone mineral density (BMD) (2, 9, 10).

The contrasting results of the various studies may be due to population differences, differences in the bone sites investigated, or sample sizes too small to accurately measure the associations of BMD with both fat and lean mass. In this article we report a study that addresses all three of these concerns in 1600 early postmenopausal women by measuring their bone mass at the hip, spine, and radius.

SUBJECTS AND METHODS

Subjects

The study subjects were participants in a multicenter, randomized, double-blind, placebo-controlled study of oral alendronate as an intervention to prevent bone loss among postmenopausal women. Study centers at four geographical locations (Nottingham, United Kingdom; Portland, OR; Honolulu; and Copenhagen) recruited subjects by using population-based strategies such as direct mailing, advertisements in the media, and telephone contacts. Strategies for recruiting varied depending on the geographical area and the local health care system. Health-maintenance organizations and other health care organizations were a common screening source for the two US centers. Researchers in the United Kingdom used the register of general practitioners. In Copenhagen, a population-based mailing list was used for Copenhagen County, a representative area of Denmark. The recruitment period was from September 1992 to June 1993. Women were eligible for the study if they met the following criteria, which were applied equally across the four study centers: were aged 45–59 y at entry; were ≥ 6 mo postmenopausal, based on a history of absence of menstrual periods during the preceding 6 mo, which

1 From the School of Public Health, University of Hawaii, Honolulu; Hawaii Osteoporosis Center, Honolulu; Merck Research Laboratories, Rahway, NJ; Center for Clinical Basic Research, Ballerup, Denmark; Nottingham City Hospital, United Kingdom; and the Center for Metabolic Bone Disorders, Portland, OR. The following are additional EPIC Study Group members: Kenneth G Faulkner, Center for Metabolic Bone Disorders; Clair Chivers and Carol Coupland, Nottingham City Hospital; and Claus Christiansen, Center for Clinical and Basic Research.

2 Supported by Merck Research Laboratories, Rahway, NJ.

3 Address reprint requests to MM Hla, Hawaii Osteoporosis Center, 401 Kamakee Street, Honolulu, HI 96814-4224.

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was confirmed by a serum follicle-stimulating hormone concentration within the postmenopausal range; were in generally good health based on medical history, physical examination, and a laboratory screening evaluation; had a lumbar spine anatomy acceptable for precise spine densitometry; had no plans to relocate during the 6-y study; had no present or past malignancy; had not used estrogen or progesterin within the past 3 mo; had no prior lifetime bisphosphonate or fluoride treatment of > 110 μmol/d (> 2 mg/24 h); had no confounding disease or treatment affecting bone (eg, active thyroid disorder or anticonvulsant use); had a serum creatinine concentration ≤ 130 μmol/L (≤ 1.5 mg/dL); and were not > 30% above ideal body weight based on Metropolitan Life Insurance tables (11). The most common reason for exclusion was menopausal status.

Of the potential participants, 2409 attended a clinic visit. Of these, 2177 entered a placebo run-in phase, which lasted 2 wk. Ultimately, 1609 women were randomly assigned to the study and took at least one dose of medication. To ensure that the majority of subjects were not osteoporotic, enrollment was restricted so that not > 10% of the subjects at any study site had a spine BMD ≤ 0.8 g/cm².

All subjects were fully informed of the study procedures and gave informed consent. The study was approved by the local ethical review committees of the four study centers.

Methods
All participants attended two baseline visits scheduled ≈2 wk apart. This study only used data from these visits, which were collected before drug therapy began. On the first visit, nurse interviewers obtained a complete history, including menstrual, reproductive, and past medical and medication histories, smoking habits, alcohol consumption, and dietary and supplemental calcium intakes. During both baseline visits, height, weight, body composition, and bone mineral contents were also measured. Height was measured to the nearest 0.1 cm by using a Harpenden stadiometer (Holtain Ltd, Crymych, United Kingdom) while subjects stood in an erect position without shoes. Body weight was measured to the nearest 0.1 kg with subjects wearing indoor clothes but no shoes. Fat mass, lean mass, and bone mineral content (BMC) were measured by dual-energy X-ray absorptiometry (DXA, Hologic 2000; Hologic Inc, Waltham, MA). Quality assurance for machines and for bone measurements was centrally controlled by the manufacturer of the machine (Hologic Inc). Quality assurance included an initial machine calibration among the four study centers before the baseline measurements and an ongoing assessment of machine performance. All operators of the machines attended training sessions conducted by Hologic Inc. The quality-assurance program included on-site and central monitoring of machine performance based on daily phantom scanning, circulation of “gold standard” phantoms, uniform software changes between sites, as well as centralized confirmation of the adequacy of all subject bone density scans.

There was no quality control of fat and lean mass measurements across study sites because there was no independent quality-control measurement software available at the time this study began. However, the manufacturer did an independent evaluation of machine performance by cross-calibrating eight DXA scanners used in another multicenter study with a circulating gold standard tissue-calibration step phantom. The expected variation of fat and lean mass measurements on the Hologic DXA scanners was as follows: an SD of 6.5 g for a fat mass of 649 g and an SD of 6.5 g for a lean mass of 1657 g. These results suggest that the intercenter variation of body composition is similar to the intercenter variation of BMD measurements.

Statistics
Statistical analyses were performed by using Statistical Analysis System (SAS) software (version 6.10; SAS Institute Inc, Cary, NC). Multiple-regression analysis (REG procedure) was performed to examine the associations between the independent variables of interest (body weight, fat mass, lean mass) and the dependent variables (BMC measurements). Age, years since menopause, height, duration (in mo) of hormonal-replacement therapy, and ethnicity [white, Asian (Japanese, Chinese, or Korean ancestry), or other] were entered as potential confounders in all analyses. Years since menopause was entered after log transformation to improve linearity. Bone area (spine and femoral sites) or bone width (radial sites) were also adjusted for in all analyses. Prentice et al (12–14) recommend adjusting for bone area or bone width and body size (weight and height), as done here, rather than dividing BMC by these values, because division may fail to correct BMC fully for bone and body size. Study center was adjusted in all analyses including the four study centers combined. Head fat mass and head lean mass were subtracted from the total body fat and lean mass measurements because measurements of soft tissue mass gain relatively little from including the head, but the errors in measuring fat and lean mass for the head are relatively large (15).

In preliminary analyses we also examined dairy intake, calcium supplementation, exercise, number of live births, history of contraceptive use, serum estradiol 1, years of cigarette smoking, and alcohol and caffeine consumption. Adjustment for these variables, however, did not substantially affect our results and these variables were dropped from the final models. Interactions between fat and lean were also tested for all models; however, none of the interactions were significant.

Regression results were expressed as the difference in BMC per interquartile range (IQR) of body weight, lean mass, or fat mass, representing the range between the 25th and 75th percentiles. We chose IQRs instead of SDs because distributions were truncated by the study design. To obtain regression results expressed as a difference per IQR, we divided the units of body weight, fat mass, and lean mass by their IQRs before undertaking the regression analyses. The regression coefficients and SEs were then converted to percentages by dividing by the mean of the BMC in the regression model. CIs were subsequently calculated from the SEs. For some analyses, subjects were cross-classified into nine groups on the basis of tertiles of fat and lean mass measurements. The cross-classified data were analyzed by using the femoral neck and spine BMC as dependent variables and adjusting for the same independent variables as before. Results from these analyses were expressed as adjusted mean BMC.

RESULTS
A total of 1600 of the 1609 eligible subjects had complete data and were included in the analyses (~400 subjects from
each study center). Nine subjects (<1%) were excluded because of missing data for one or more of the study variables. Characteristics of the participants are summarized in Table 1. Except for the women from Hawaii, the subjects were predominantly white. In Hawaii, 44% of the subjects were white, 42% were Asian, and 14% were from other ethnic groups. About 31% of the study subjects had a history of estrogen use (median: 9 mo of use).

On multiple-regression analysis, body weight was positively associated with BMC at all bone sites examined and among women from all four study centers (Table 2). The differences in BMC per IQR of body weight were greatest at the femoral sites (ranging from 5% to 10%). The differences at the spine (ranging from 4% to 7%) and ultradistal radius (ranging from 6% to 8%) were greater than at the midradius (ranging from 2% to 3%) and lower one-third radius sites (ranging from 1% to 3%). Except for the lower one-third radius for the Hawaii study center, the associations were all significant at the 5% level.

When multiple-regression analyses were repeated by substituting whole-body fat mass and lean mass for body weight, both fat mass (Table 3) and lean mass (Table 4) had independent associations with bone mass. However, the magnitude of associations varied at the different bone sites. The associations of fat mass were positive and significant across the four study centers for the hip, spine, and ultradistal radius bone sites (Table 3). The ranges in differences of BMC per IQR of fat mass were 3–7% at the hip sites, 4–5% at the spine site, and 4–6% at the ultradistal radius site. At the hip the magnitude of the association was greatest at the Ward's triangle. At the midradius site BMC differed only in the range of 1–3% per IQR of fat mass. The association at the midradius site was significant for all subjects combined but not for all study centers. At the lower one-third of the radius the association was not significant, even when data for all subjects was combined.

The difference in BMC per IQR of lean mass was greatest at the hip sites, especially at the neck and trochanter (ranging from 3% to 9%), and the hip associations were consistently positive across the study centers (Table 4). At the lower one-third and midradius, there were significant but weaker associations with lean mass (ranging from 2% to 3%) at all study centers except Hawaii. At the spine and ultradistal radius, the positive associations were significant for all subjects combined, but not for every study center.

In Hawaii, unlike other study centers, the BMC difference per IQR of lean mass was close to zero at the midradius and ultradistal radius (Table 4). When separate analyses were performed for whites and Asians from the Hawaii center, the associations at the midradius and ultradistal radius were positive for whites (an increase of ~1% in BMC per IQR of lean mass) and negative for Asians (a 1–2% decrease in BMC per IQR increase in lean mass). The differences between the whites and Asians, however, were not significant.

When the associations of fat mass (Table 3) and lean mass (Table 4) were compared for the various bone sites, fat mass had stronger associations at the spine, ultradistal radius, and Ward’s triangle, whereas lean mass had stronger associations for the femoral neck, trochanter, and lower one-third radius. No remarkable differences in effects were apparent at the midradius and Ward’s triangle.

Given the multiple analyses that were performed, there is a possibility that some significant results could be due to chance. However, given the distance of most of the CIs from zero, and the consistency of the results across study centers, it is unlikely that an adjustment for multiple comparisons would substantially alter the conclusions.

The combined influences of fat and lean mass were examined graphically at the femoral neck (Figure 1) and spine sites (Figure 2). At the femoral neck, for each level of fat mass, there was a consistent increase in BMC across the strata of lean mass, and for each level of lean mass there was a consistent increase in BMC across the strata of fat mass. At the spine, for each level of lean mass, there was also a consistent increase in BMC across the strata of fat mass. The increases in spine BMC across the strata of fat mass were also consistent, except for the lowest level of fat mass, for which the BMC values for the lowest and middle thirds of lean mass were comparable, yet well below the highest third.

**DISCUSSION**

This study showed that both the fat and lean components of body weight had independent influences on BMC. With only a few exceptions, the associations were similar in direction and comparable in magnitude for our subjects from Nottingham, Portland, Hawaii, and Copenhagen. This study further showed that the relative influence of fat and lean mass depends on the bone site studied.

Body weight itself had strong influences on most bone sites. Strong associations occurred at both weight-bearing (hip and

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**TABLE 1**

Characteristics of the 1600 postmenopausal study subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All centers (n = 1600)</th>
<th>Nottingham (n = 418)</th>
<th>Portland (n = 398)</th>
<th>Hawaii (n = 386)</th>
<th>Copenhagen (n = 398)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>54 (51, 56)</td>
<td>54 (50, 56)</td>
<td>52 (50, 55)</td>
<td>53 (50, 56)</td>
<td>55 (52, 57)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.7 (59.3, 73.6)</td>
<td>65 (59.0, 72.5)</td>
<td>69.7 (62.5, 77.3)</td>
<td>61.6 (55.5, 69.3)</td>
<td>67 (60.5, 75)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.5 (158.1, 166.8)</td>
<td>161.3 (157.0, 165.5)</td>
<td>164.2 (160.1, 168.0)</td>
<td>159.8 (155.0, 164.3)</td>
<td>164.5 (160.3, 168.2)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8 (22.6, 27.6)</td>
<td>24.9 (23.1, 27.7)</td>
<td>25.8 (23.1, 28.6)</td>
<td>24.2 (21.9, 26.9)</td>
<td>24.6 (22.3, 27.5)</td>
</tr>
<tr>
<td>Years since menopause (y)</td>
<td>4.8 (2.0, 9.2)</td>
<td>5.2 (2.3, 9.5)</td>
<td>4.2 (1.6, 9.9)</td>
<td>3.5 (1.3, 9.2)</td>
<td>5.4 (3.0, 8.4)</td>
</tr>
<tr>
<td>Whole-body fat (kg)²</td>
<td>25.4 (20.6, 31.7)</td>
<td>26.0 (21.7, 32.2)</td>
<td>28.0 (22.2, 33.7)</td>
<td>23.4 (18.9, 29.2)</td>
<td>25.1 (19.8, 31.1)</td>
</tr>
<tr>
<td>Whole-body lean (kg)²</td>
<td>33.4 (30.7, 36.6)</td>
<td>32.7 (30.2, 35.5)</td>
<td>34.6 (31.9, 37.5)</td>
<td>31.1 (28.5, 34.2)</td>
<td>35.3 (32.5, 37.8)</td>
</tr>
</tbody>
</table>

1 Median (and 25th and 75th percentiles).
2 Values exclude the head.
TABLE 2
Percentage differences in bone mineral content of bone sites per interquartile range in body weight

<table>
<thead>
<tr>
<th>Bone site</th>
<th>Study center</th>
<th>All centers (n = 1600)</th>
<th>Nottingham (n = 418)</th>
<th>Portland (n = 398)</th>
<th>Hawaii (n = 386)</th>
<th>Copenhagen (n = 398)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Femoral neck</td>
<td></td>
<td>7.46 (6.51, 8.40)</td>
<td>8.38 (6.40, 10.36)</td>
<td>5.58 (4.79, 7.38)</td>
<td>9.25 (7.39, 12.7)</td>
<td>7.66 (5.74, 9.58)</td>
</tr>
<tr>
<td>Trochanter</td>
<td></td>
<td>7.76 (6.75, 8.76)</td>
<td>7.43 (6.52, 9.60)</td>
<td>6.23 (5.27, 8.20)</td>
<td>9.07 (7.08, 11.8)</td>
<td>8.56 (6.68, 10.4)</td>
</tr>
<tr>
<td>Hip, Ward’s triangle</td>
<td></td>
<td>8.56 (7.10, 10.0)</td>
<td>9.96 (8.67, 13.1)</td>
<td>5.46 (4.67, 8.24)</td>
<td>10.41 (7.36, 13.5)</td>
<td>9.77 (8.48, 12.7)</td>
</tr>
<tr>
<td>Spine</td>
<td></td>
<td>5.68 (4.78, 6.59)</td>
<td>5.34 (3.89, 7.47)</td>
<td>4.27 (2.72, 5.82)</td>
<td>7.59 (5.63, 9.55)</td>
<td>6.50 (4.69, 8.31)</td>
</tr>
<tr>
<td>Midradius</td>
<td></td>
<td>2.78 (2.12, 3.45)</td>
<td>2.92 (1.63, 4.21)</td>
<td>2.87 (1.60, 4.14)</td>
<td>1.77 (0.92, 2.35)</td>
<td>3.25 (1.45, 4.83)</td>
</tr>
<tr>
<td>Lower one-third of radius</td>
<td></td>
<td>1.92 (1.31, 2.53)</td>
<td>1.72 (0.57, 2.87)</td>
<td>1.83 (0.72, 2.39)</td>
<td>0.83 (0.47, 1.21)</td>
<td>3.03 (1.69, 4.38)</td>
</tr>
<tr>
<td>Ultradistal radius</td>
<td></td>
<td>6.75 (5.79, 7.72)</td>
<td>7.89 (5.81, 9.97)</td>
<td>5.84 (4.11, 7.57)</td>
<td>6.20 (4.28, 8.12)</td>
<td>7.55 (5.50, 9.60)</td>
</tr>
</tbody>
</table>

Percentage differences per interquartile range in body weight; 95% CIs in parentheses. All analyses were adjusted for age, years since menopause, height, estrogen use, bone area or width, study center (for all subjects combined), and ethnicity.

FAT, LEAN, AND BONE MASS

TABLE 3
Percentage differences in bone mineral content of bone sites per interquartile range in whole-body fat mass

<table>
<thead>
<tr>
<th>Bone site</th>
<th>Study center</th>
<th>All centers (n = 1600)</th>
<th>Nottingham (n = 418)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Femoral neck</td>
<td></td>
<td>4.05 (3.09, 5.00)</td>
<td>5.02 (3.05, 6.99)</td>
<td>2.48 (0.62, 4.33)</td>
<td>4.69 (2.71, 6.67)</td>
<td>4.53 (2.62, 6.44)</td>
</tr>
<tr>
<td>Trochanter</td>
<td></td>
<td>4.22 (3.20, 5.25)</td>
<td>4.46 (3.20, 6.62)</td>
<td>3.10 (1.04, 5.15)</td>
<td>4.57 (2.39, 6.76)</td>
<td>4.95 (3.08, 6.83)</td>
</tr>
<tr>
<td>Hip, Ward’s triangle</td>
<td></td>
<td>5.60 (4.12, 7.10)</td>
<td>7.70 (4.63, 10.78)</td>
<td>3.33 (0.42, 6.24)</td>
<td>5.34 (2.17, 8.50)</td>
<td>6.62 (3.75, 9.50)</td>
</tr>
<tr>
<td>Spine</td>
<td></td>
<td>4.17 (3.24, 5.10)</td>
<td>4.23 (2.27, 6.18)</td>
<td>3.77 (2.09, 5.44)</td>
<td>5.11 (3.06, 7.17)</td>
<td>4.39 (2.56, 6.21)</td>
</tr>
<tr>
<td>Midradius</td>
<td></td>
<td>1.67 (1.01, 2.33)</td>
<td>1.57 (0.31, 2.84)</td>
<td>1.18 (0.00, 2.49)</td>
<td>2.65 (0.27, 3.83)</td>
<td>2.20 (0.82, 3.58)</td>
</tr>
<tr>
<td>Lower one-third of radius</td>
<td></td>
<td>0.59 (0.02, 1.21)</td>
<td>0.09 (0.01, 0.22)</td>
<td>0.47 (0.06, 1.61)</td>
<td>0.17 (0.00, 1.52)</td>
<td>1.47 (0.16, 2.78)</td>
</tr>
<tr>
<td>Ultradistal radius</td>
<td></td>
<td>5.35 (4.38, 6.33)</td>
<td>5.56 (3.52, 7.60)</td>
<td>4.30 (2.47, 6.12)</td>
<td>5.98 (4.00, 7.96)</td>
<td>5.96 (3.99, 7.94)</td>
</tr>
</tbody>
</table>

Percentage differences per interquartile range in whole-body fat mass; 95% CIs in parentheses. All analyses were adjusted for whole-body lean mass, age, years since menopause, height, estrogen use, bone area or width, study center (for all subjects combined), and ethnicity.
Our findings that both fat and lean mass influence bone mass agree with the findings of the California study by Edelstein and Barrett-Connor (2), the Michigan study by Sowers et al (9), and the Cambridge study by Compston et al (10). However, Edelstein and Barrett-Connor concluded that the effect of fat mass was stronger at the total hip and the neck of femur, whereas the effect of lean mass was stronger at the lumbar spine, trochanter, middle and ultradistal radius. This conclusion is somewhat different from our results. In their study, the comparison of the relative influence of fat and lean mass was based on the percentages of variance explained by fat and lean mass, which would depend on the distribution of lean and fat mass in their population. At the femoral neck, the difference in variance explained by fat and lean mass in their study was only 0.9%. The differences between studies could in part result from the different ages of the participants. The study of Edelstein and Barrett-Connor included older postmenopausal women (aged 55–84 y), whereas our study was restricted to younger

### TABLE 4

Percentage differences in bone mineral content of bone sites per interquartile range in whole-body lean mass

<table>
<thead>
<tr>
<th>Bone site</th>
<th>All centers (n = 1600)</th>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td></td>
<td>%</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>6.21 (4.99, 7.42)</td>
<td>6.34 (3.87, 8.08)</td>
<td>5.34 (2.95, 7.73)</td>
<td>8.25 (5.89, 10.60)</td>
<td>5.99 (3.43, 8.54)</td>
</tr>
<tr>
<td>Trochanter</td>
<td>6.50 (5.19, 7.80)</td>
<td>5.61 (2.89, 8.33)</td>
<td>5.33 (2.70, 7.96)</td>
<td>9.26 (6.67, 11.85)</td>
<td>7.07 (4.53, 9.60)</td>
</tr>
<tr>
<td>Hip, Ward’s triangle</td>
<td>5.08 (3.21, 6.96)</td>
<td>3.91 (0.08, 7.75)</td>
<td>3.25 (-0.44, 6.93)</td>
<td>8.96 (5.22, 12.71)</td>
<td>5.89 (2.08, 9.70)</td>
</tr>
<tr>
<td>Spine</td>
<td>2.51 (1.32, 3.70)</td>
<td>1.75 (-0.74, 4.25)</td>
<td>0.54 (-1.59, 2.69)</td>
<td>4.51 (2.07, 6.96)</td>
<td>3.87 (1.41, 6.34)</td>
</tr>
<tr>
<td>Midradius</td>
<td>1.92 (1.04, 2.80)</td>
<td>2.36 (0.69, 4.02)</td>
<td>2.78 (1.03, 4.52)</td>
<td>.005 (-1.71, 1.72)</td>
<td>2.41 (0.45, 4.37)</td>
</tr>
<tr>
<td>Lower one-third of radius</td>
<td>2.37 (1.54, 3.18)</td>
<td>2.94 (1.46, 4.42)</td>
<td>2.24 (0.69, 3.78)</td>
<td>1.04 (-0.65, 2.73)</td>
<td>3.14 (1.29, 4.50)</td>
</tr>
<tr>
<td>Ultradistal radius</td>
<td>2.38 (1.07, 3.68)</td>
<td>4.18 (1.51, 6.84)</td>
<td>2.40 (-0.05, 4.86)</td>
<td>0.34 (-2.09, 2.78)</td>
<td>3.21 (0.27, 6.14)</td>
</tr>
</tbody>
</table>

*Percentage differences per interquartile range in whole-body lean mass; 95% CIs in parentheses. All analyses were adjusted for whole-body fat mass, age, years since menopause, height, estrogen use, bone area or width, study center (for all subjects combined), and ethnicity.*

**FIGURE 1.** Mean bone mineral content (BMC) of the femoral neck by thirds of fat and lean mass among postmenopausal women from Nottingham, United Kingdom; Portland, OR; Honolulu; and Copenhagen, 1992–93. The analysis was adjusted for age, years since menopause, height, estrogen use, bone area, study center, and ethnicity. Sample sizes for each group from left to right, beginning with the front row, were 117, 173, 243, 143, 196, 195, 273, 165, and 95. The cutoff points of fat mass were 22.4 and 29.4 kg. The cutoff points of lean mass were 31.6 and 35.5 kg.
FIGURE 2. Mean bone mineral content (BMC) of the lumbar spine by thirds of fat and lean mass among postmenopausal women from Nottingham, United Kingdom; Portland, OR; Honolulu; and Copenhagen, 1992–93. The analysis was adjusted for age, years since menopause, height, estrogen use, bone area, study center, and ethnicity. Sample sizes for each group from left to right, beginning with the front row, were 117, 173, 243, 143, 196, 195, 273, 165, and 95. The cutoff points of fat mass were 22.4 and 29.4 kg. The cutoff points of lean mass were 31.6 and 35.5 kg.

postmenopausal women (aged 45–59 y). Measurement techniques also differed between the studies. Edelstein and Barrett-Connor measured body composition using bioelectrical impedance, whereas we used DXA measurements. Sowers et al concluded, as our results suggest, that lean mass has a stronger association than fat mass with bone mass at the femoral neck and trochanter. Their study used DXA measurements, but was of premenopausal women. Compston et al reported stronger associations of fat mass than lean mass with both hip and spine sites. Their study included only 97 postmenopausal women and their analyses were adjusted only for age. Other studies reported that either fat mass alone (5) or lean mass alone (7) were associated with the hip, spine, or radius sites. These studies were all smaller than ours and they may have lacked the sample size to measure the independent effects of fat and lean mass.

Our study shows the effects of total body composition (whole-body fat and lean mass) at specific bone sites. For fat mass, the sites with the strongest associations—the spine and distal radius—are not exceptionally high-adipose sites. Total body fat mass rather than regional fat mass may most effect these bone sites. On the contrary, regional lean mass may exert strong effects on bone mass locally. For example, the hip, a highly muscular site, showed significant lean mass associations. Similarly, except at the Hawaii center, the radial sites showed significant associations with lean mass. Lean mass, which to a large extent is muscle mass, may increase dynamic loading through muscular contraction. The hypertrophy in radial bone mass in the dominant arms of tennis players supports this hypothesis (24, 25).

The main limitation of our study was the cross-sectional design. Our findings will require confirmation in a longitudinal study. There are also limitations of using DXA as we have done, for measuring fat and lean mass. For instance, the hydration of lean mass is assumed fixed and uniform throughout the body, which is true only for a healthy population. Measurement errors can arise if study subjects are sick or very young or very old (15). However, our study included only healthy, early postmenopausal women; thus measurement errors should have been minimal.

Affecting the interpretation of the results is exclusion of women who were > 30% above their ideal body weight; as a consequence, both the relative and absolute effects of fat and lean mass on bone mass may be different at extreme body weight than for the subjects in this study. Generalization from our results to other populations should be limited to the ranges of lean and fat mass in our population. Within these ranges of fat and lean mass, differences in BMC per IQR were often small (< 5%), although significant. However, results from longitudinal studies suggest that a 5% difference in BMD corresponds to a 17–24% increase in fracture risk (26, 27). For women at the ends of the distributions of fat or lean mass, or both, the differences in BMC would be > 5%. In clinical trials, 5–10% differences in BMD were associated with twofold differences in fracture risk (28). Although it is uncertain from our
cross-sectional study to what extent the associations of fat and lean mass with bone mass may persist into older ages (when fracture risk is higher), it appears that differences in lean and fat mass may be associated with significant differences in risk.

The strength of our study was the large sample size, with 1600 women from four geographical locations. Larger sample sizes provide more precise estimates and greater statistical significance. Including four geographical locations enabled us to compare the consistency of the associations. In addition, we used standardized DXA machines and we centralized quality control of bone measurements to minimize inter- and intrindividual variation.

Overall, our findings were consistent across the four study centers; however, there was some variability in the results. A difference noted in the influence of lean mass at the radius between Hawaii and other study centers could be due to ethnic differences. Even among the predominantly white study centers, however, the magnitude of the associations varied. Thus, there may have been heterogeneity among whites from the different geographical locations. For instance, in Portland, the magnitude of many associations was lower than that of other study centers. However, the 95% CIs for all centers overlapped. The directions of the associations for Portland were similar to those for other study centers, and the lower magnitude of the associations for Portland do not alter our general conclusions.

We conclude that both fat and lean mass have independent influences on bone mass that cannot be simply explained by differences in mechanical loading. Our results suggest that the relative influence of fat and lean mass varies across bone sites, varying with the content of trabecular bone and the physical mobility and muscularity of the site.

REFERENCES