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Low Body Mass Index Is an Important Risk Factor for Low Bone Mass and Increased Bone Loss in Early Postmenopausal Women*

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ABSTRACT

Thinness (low percentage of body fat, low body mass index [BMI], or low body weight) was evaluated as a risk factor for low bone mineral density (BMD) or increased bone loss in a randomized trial of alendronate for prevention of osteoporosis in recently postmenopausal women with normal bone mass (n = 1609). The 2-year data from the placebo group were used (n = 417). Percentage of body fat, BMI, and body weight were correlated with baseline BMD (r = −0.13 to −0.43, $p < 0.01$) and 2-year bone loss (r = −0.14 to −0.19, $p < 0.01$). Women in the lowest tertiles of percentage of body fat or BMI had up to 12% lower BMD at baseline and a more than 2-fold higher 2-year bone loss as compared with women in the highest tertiles ($p \leq 0.004$). Women with a lower percentage of body fat or BMI had higher baseline levels of urine N-telopeptide cross-links (r = −0.24 to −0.31, $p < 0.0001$) and serum osteocalcin (r = −0.12 to −0.15, $p < 0.01$). To determine if the magnitude of treatment effect of alendronate was dependent on these risk factors, the group treated with 5 mg of alendronate was included (n = 403). There were no associations between fat mass parameters and response to alendronate treatment, which indicated that risk of low bone mass and increased bone loss caused by thinness could be compensated by alendronate treatment. In conclusion, thinness is an important risk factor for low bone mass and increased bone loss in postmenopausal women. Because the response to alendronate treatment is independent of fat mass parameters, prevention of postmenopausal osteoporosis can be equally achieved in thinner and heavier women. (J Bone Miner Res 1999; 14:1622–1627)

INTRODUCTION

OSTEOPOROSIS IS A COMMON DISEASE that affects up to one third of postmenopausal women.[1,2] The estimated cost for treatment of osteoporotic fractures is more than 13 billion U.S. dollars per year.[3] Because of the aging of the population and subsequent increase over time in the incidence of fractures, these already huge costs are expected to more than double over the next 30 years,[4] unless comprehensive programs for prevention and treatment are initiated. To substantiate future recommendations and optimize public health strategies, a better understanding of the impact of various risk factors for osteoporosis is crucial.

The existence of a positive association between body size and bone mass is well established.[5–10] Moreover, low body mass index (BMI) has been shown to be a predictor of increased bone loss at the forearm.[11] However, the association at other skeletal regions between BMI, bone mass, and bone loss remains to be determined. The potential impact of thinness on the development of postmenopausal osteoporosis is particularly relevant because of the high incidence of malnutrition in the developing countries and be-

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cause slimness is promoted as the ideal in industrialized countries.

In the present study, we evaluated thinness (low percentage of body fat, low BMI, or low body weight) as a risk factor for low bone mineral density (BMD) or increased bone loss in a population of recently postmenopausal women with normal bone mass participating in a randomized trial of alendronate treatment for prevention of postmenopausal osteoporosis ($n = 1609$). Also, we analyzed whether the treatment effect of alendronate was dependant on these risk factors.

MATERIALS AND METHODS

Subjects

The Early Postmenopausal Intervention Cohort (EPIC) study is an ongoing randomized, double-blind, placebo-controlled trial of the efficacy and safety of daily oral alendronate treatment for prevention of postmenopausal osteoporosis.[12] The study is being carried out at four centers (Copenhagen County, Denmark; Nottingham, U.K.; Honolulu, HI, U.S.A.; and Portland, OR, U.S.A.) with a total of 1609 enrolled participants. All participants were 45–59 years of age and at least 6 months past menopause at baseline, in good general health, and without clinical or laboratory evidence of confounding systemic disease. Women with a baseline body weight above 130% of the ideal as defined by the Metropolitan Health Insurance Company, and who had a body thickness exceeding either 22.5 cm (9 in) in the anteroposterior projection of the spine, or 30 cm (12 in) in the lateral projection, were excluded from the study, since greater levels of obesity may result in inaccuracies of the BMD measurements. Women with a low dietary calcium intake (below 500 mg daily calcium) were advised to increase their daily calcium intake. However, calcium supplements were not included in the protocol, more closely reflecting routine clinical practice. At baseline, the participants were randomized to treatment with placebo, alendronate 2.5 mg, or alendronate 5 mg (Merck Research Laboratories, Rahway, NJ, U.S.A.). The present analyses included participants in the placebo group who had spinal BMD measurements available at baseline and at year 2 ($n = 417$). To analyze the influence of fat mass parameters on the response to alendronate treatment, we used the group treated with alendronate 5 mg ($n = 403$).

The protocol was approved by the local ethics committees and institutional review boards. All participants consented in writing after having been provided with oral and written information regarding the study.

Methods

Bone densitometry: Measurements of BMD at the lumbar spine (L1–L4), total hip, total body, and forearm (the one third–distal region, which consists of mainly cortical bone, and the ultra-distal region, which consists of mainly trabecular bone) were performed at baseline and annually thereafter by dual-energy X-ray absorptiometry (Hologic 2000; Hologic, Waltham, MA, U.S.A.). A maximum of 10% of study participants at each center were allowed to have a baseline spine BMD T score below –2 SD of the premenopausal mean, peak value (corresponding to a spine BMD above 0.8 g/cm^2). Percentage of body fat was derived from the total body composition measurements of the total body scans. Body weight was measured at baseline and every 6 months thereafter. Information regarding age and the number of years since menopause was obtained at baseline. The short-term precision errors for measurements of BMD and percentage of body fat ranged between 0.7% and 1.9%.

Table 1. Baseline Demographic Data and Fat Mass Parameters in the Study Groups

Treatment	*Placebo* (n = *417*)	*Alendronate 5 mg* (n = *403*)
Age (years)	53.0 ± 3.6	53.4 ± 3.8
YSM (years)	5.6 ± 5.4	5.2 ± 4.6
Height (cm)	162.0 ± 6.5	161.8 ± 6.5
Weight (kg)	66.7 ± 10.4	66.6 ± 10.2
BMI (kg/cm^2)	25.4 ± 3.6	25.4 ± 3.5
Percentage of body fat (%)	40.1 ± 6.7	40.1 ± 6.6
Spine BMD (g/cm^2)	0.96 ± 0.13	0.94 ± 0.12

YSM, years since menopause; BMI, body mass index.

Biochemical parameters: Blood and second morning void urine samples were collected after an overnight fast at baseline and every 6 months thereafter. Serum osteocalcin (OC) was measured by a radioimmunoassay (Human Osteocalcin Kit; Nichols Institute, San Juan Capistrano, CA, U.S.A.).[13] Urinary N-telopeptide cross-links of type I collagen (NTX) was measured by an enzyme-linked immunosorbent assay (Osteomark™; Ostex, Seattle, WA, U.S.A.)[14] and corrected for creatinine excretion.

Statistical analysis

Current SAS Institute procedures were used for statistical analysis. Mean values and SD were calculated as parametric measures of location and dispersion. Multiple regression was used to examine the relationships between fat mass parameters and bone mass. For some of the analyses, the study population was divided by tertiles of fat mass parameters or by years since menopause. To eliminate interindividual variance, changes in bone mass were expressed as the percentage change from baseline for each subject. Significance was accepted at the $p \leq 0.05$ level.

RESULTS

The baseline demographic characteristics, spine BMD, and fat mass parameters for the placebo group did not differ from the group treated with alendronate 5 mg (Table 1).

Baseline BMD correlated with percentage of body fat, BMI, and body weight (Table 2). These coefficients of correlation were not significantly affected by age at baseline or years since menopause and were stronger for BMI than for percentage of body fat. In addition, the correlations between fat mass parameters and baseline BMD were stronger at the spine and hip than at the total body and forearm. Women in the lowest tertiles of percentage of body fat or

TABLE 2. COEFFICIENTS OF CORRELATION BETWEEN FAT MASS PARAMETERS AND BASELINE BMD IN THE PLACEBO GROUP ($N = 417$)

Regional BMD	*Spine BMD*	*Hip BMD*	*Total body BMD*	*One third–distal forearm BMD*	*Ultra-distal forearm BMD*
Percentage of body fat	−0.13*	−0.23†	0.01	−0.04	−0.26†
Body mass index	−0.27†	−0.41†	−0.16†	−0.11‡	−0.31†
Body weight	−0.33†	−0.43†	−0.28†	−0.21†	−0.30†

* $p < 0.01$; † $p < 0.001$; ‡ $p < 0.05$.

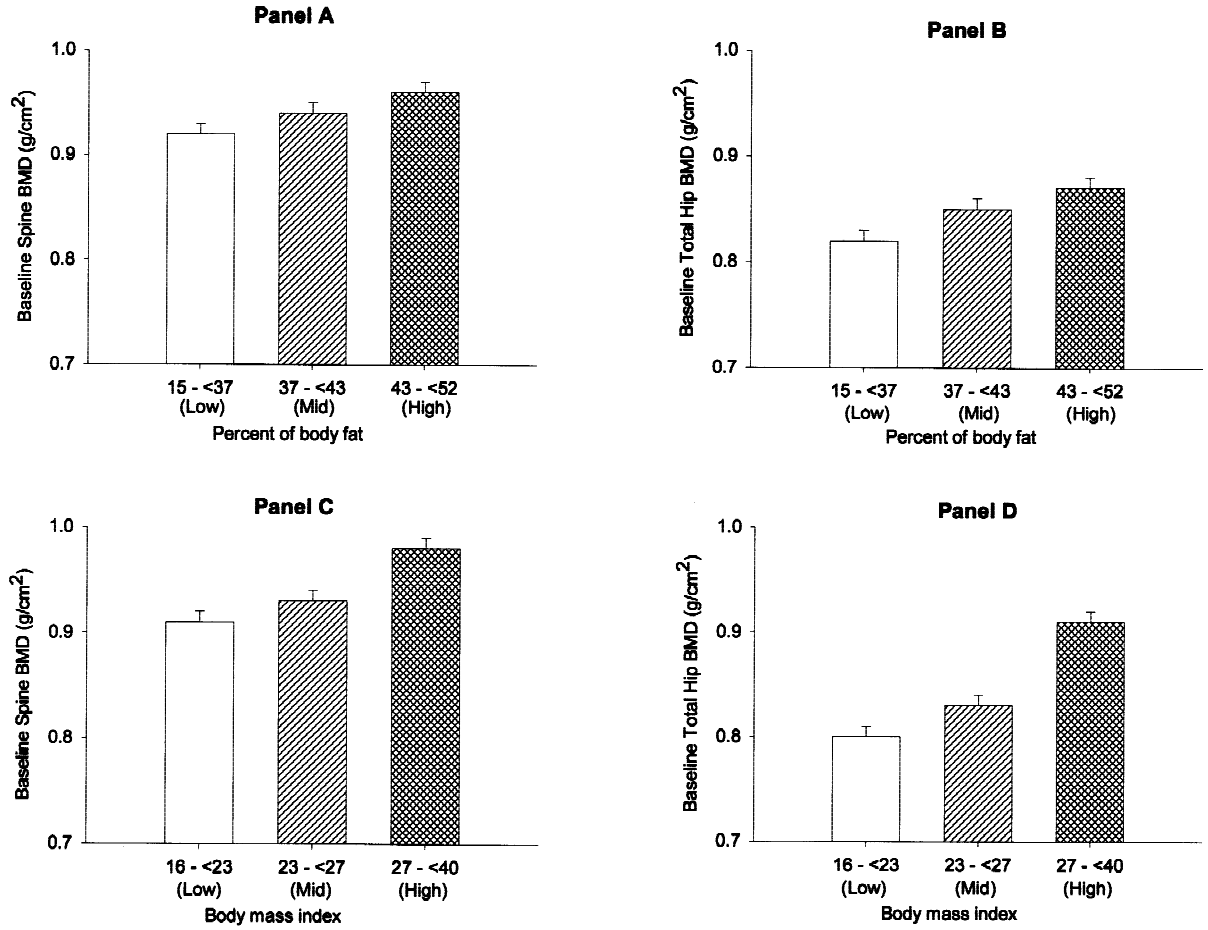

FIG. 1 Baseline spine (A, C) and total hip (B, D) BMD (mean ± SEM) by tertiles of percentage of body fat (A, B) and of BMI (C, D) (placebo group only, $n = 417$). $p < 0.0001$ for all associations.

BMI had up to 12% lower baseline spine and hip BMD as compared with those in the highest tertiles ($p < 0.001$) (Fig. 1).

Change from baseline at year 2 in BMD correlated with percentage of body fat, BMI, and body weight (Table 3). These coefficients of correlation were not significantly affected by age at baseline or years since menopause. Women in the lowest tertiles of percentage of body fat or BMI had approximately a 2-fold greater bone loss at the spine and hip as compared with those in the highest tertiles ($p < 0.001$) (Fig. 2).

Figure 3 shows the change from baseline at year 2 in spine and hip BMD by tertiles of BMI and years since menopause. All women experienced a greater bone loss during early versus late postmenopause. Within each tertile of years since menopause, women in the lowest tertile of BMI had an approximately 2-fold greater bone loss at the spine and hip as compared with women in the highest tertile ($p \leq 0.004$). Similar results were found if percentage of body fat were used (data not shown).

Women with a lower percentage of body fat or BMI had higher baseline levels of urine NTX ($r = -0.24$ to -0.31, $p < 0.0001$) and serum OC ($r = -0.12$ to $r = -0.15$, $p < 0.01$). There were no significant associations between years since menopause and baseline NTX or OC.

Table 4 reports, by tertiles of fat mass parameters and of

TABLE 3. COEFFICIENTS OF CORRELATION BETWEEN FAT MASS PARAMETERS AND CHANGE FROM BASELINE AT YEAR 2 IN BMD IN THE PLACEBO GROUP ($N = 417$)

Regional BMD	*Spine BMD*	*Hip BMD*	*Total body BMD*	*One third–distal forearm BMD*	*Ultra-distal forearm BMD*
Percentage of body fat	–0.18*	–0.14†	–0.10‡	–0.15†	–0.08
Body mass index	–0.19*	–0.14†	–0.12†	–0.17*	–0.11‡
Body weight	–0.16*	–0.09	–0.06	–0.16*	–0.08

* $p < 0.001$; † $p < 0.01$; ‡ $p < 0.05$.

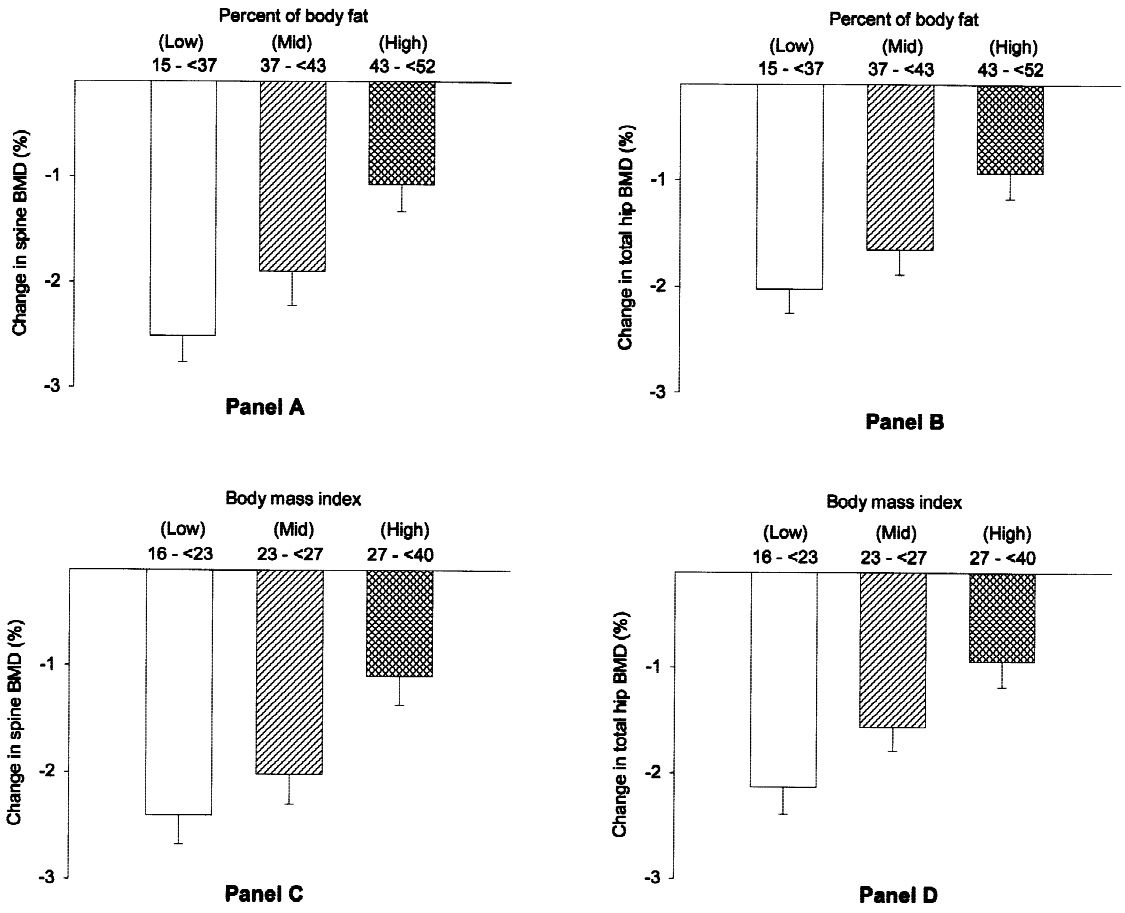

FIG. 2. Percentage change from baseline at year 2 in spine (A, C) and total hip (B, C) BMD (mean ± SEM) by tertiles of percentage of body fat (A, B) and of BMI (C, D) (placebo group only, $n = 417$). $p < 0.0001$ for all associations.

years since menopause, the percentage change from baseline at year 2 in spine and hip BMD in the group treated with alendronate 5 mg corrected for the respective bone loss in the placebo group. These corrected percentage changes were independent of BMI and of percentage of body fat measured at baseline. There was an association between these corrected percentage changes and years since menopause: $p = 0.023$ for changes in BMD at the spine and $p = 0.002$ for changes in BMD at the hip. The corrected changes were greater in women closer to the menopause than women further past the menopause. All of the corrected changes were significantly greater than zero.

DISCUSSION

This prospective study consistently demonstrated the existence of a significant association between thinness, low bone mass, and increased postmenopausal bone loss. The associations between low fat mass parameters, low bone mass, and an increased rate of bone loss were independent of age or years since menopause. However, as expected, there was an association between years since menopause and bone loss, with women closer to the menopause experiencing a greater bone loss than women further past the menopause. The present results, based on 2 years of follow-

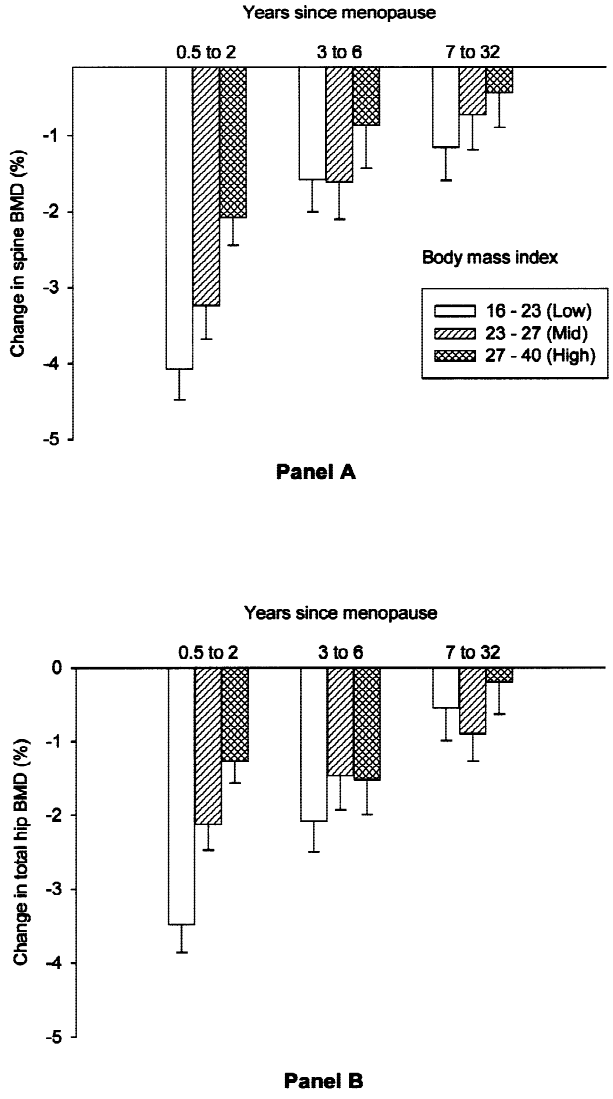

FIG. 3. Percentage change from baseline at year 2 in spine (A) and total hip (B) BMD (mean ± SEM) by tertiles of BMI and years since menopause (placebo group only, $n = 417$). $p < 0.001$ for associations with changes in spine BMD. $p = 0.004$ for associations with changes in hip BMD.

up, were statistically significant and consistent in all regions of the skeleton.

Low bone mass and increased rate of bone loss add to an increased risk of subsequent development of postmenopausal osteoporosis. Women in the lowest tertile of BMI or percentage of body fat were osteopenic at baseline with a spine BMD below –1 SD of the premenopausal mean, peak value (which corresponds to about 0.93 g/cm^2),[15,16] and exhibited a 4% bone loss at the spine over a 2-year period. Therefore, by extrapolation, a substantial proportion of these women are likely to develop postmenopausal osteoporosis before the age of 65 years. However, longitudinal data, which will be provided in the future by this ongoing study, are needed to further substantiate this conclusion.

There was a significant negative association between baseline bone turnover and percentage of body fat or BMI. Because high bone turnover is associated with increased bone loss,[17] this is compatible with the greater 2-year bone loss presently observed in women with low percentage of body fat or BMI. Serum estradiol was measured at baseline to confirm postmenopausal status before study entry. The measurement was aimed at categorizing menopausal status rather than an exact determination of the serum estradiol concentration. Furthermore, different assays were used at each of the four study centers with no cross-calibration. With these limitations, we found no consistent associations between serum estradiol, fat mass parameters, and BMD in the present study.

At each skeletal region, there was a somewhat stronger correlation between BMI and baseline BMD than between percentage of body fat and baseline BMD. Furthermore, the strength of the correlation between BMI and BMD was: hip > spine > forearm. These findings suggest a positive effect of body weight per se on BMD as compared with percentage of body fat, which was more evident at weight-bearing skeletal regions, such as the spine and hip, as compared with the forearm. Although both BMI and percentage of body fat were significantly correlated with baseline BMD, <17% of the variance in fat mass parameters accounted for the variance in baseline BMD. This was an expected finding, since BMD is a multifactorial parameter influenced by a large number of factors in addition to fat mass parameters, such as genetic background (peak bone mass) and life style.

Treatment with 5 mg of alendronate per day caused a positive response in BMD in each tertile of BMI or percentage of body fat, with no associations between response to alendronate treatment and fat mass parameters. This indicated that the deleterious influence of low percentage of body fat or BMI upon the risk of osteoporosis could be compensated for by alendronate treatment.

Alendronate is immediately taken up by the bone after gastrointestinal absorption[18] and cleared from the body without significant accumulation in any other tissue besides bone.[19,20] The antiresorptive effect is therefore not expected to be influenced by the amount of fat tissue per se, consistent with our present observations.

Finally, we observed an increase in BMD during alendronate treatment in each of the tertiles of years since menopause, although the magnitude of the increase was smaller in women closer to the menopause. This was consistent with an underlying greater bone loss in this group, presently observed in the placebo group, and also reported by others.[21,22]

In conclusion, postmenopausal women with lower BMI exhibit low bone mass and rapid bone loss, both of which are independent contributing factors to an increased risk of postmenopausal osteoporosis. Thinner women, despite a normal bone mass at menopause, are at increased risk of developing postmenopausal osteoporosis within 1–2 decades after the menopause. Because the response to alendronate treatment is independent of fat mass parameters, prevention of postmenopausal osteoporosis can be equally achieved in thinner and heavier women.

TABLE 4. CHANGE FROM BASELINE AT YEAR 2 IN BMD BY TERTILES OF PERCENTAGE OF FAT MASS PARAMETERS, AND YEARS SINCE MENOPAUSE IN THE GROUP TREATED WITH ALENDRONATE 5 MG CORRECTED FOR THE RESPECTIVE BONE LOSS IN THE PLACEBO GROUP

	*Tertiles of percentage of body fat (%)**		
	15–<37	37–<43	43–52
Change in spine BMD	5.50 ± 0.27	5.94 ± 0.30	4.79 ± 0.30
Change in hip BMD	3.58 ± 0.21	3.70 ± 0.23	3.04 ± 0.21
	*Tertiles of BMI (kg/cm^2)**		
	16–<23	23–<27	27–40
Change in spine BMD	5.35 ± 0.26	5.94 ± 0.30	5.07 ± 0.30
Change in hip BMD	3.68 ± 0.20	3.66 ± 0.26	3.13 ± 0.20
	Tertiles of years since menopause (years)[†]		
	0.5–<3	3–<7	7–32
Change in spine BMD	5.80 ± 0.29	5.45 ± 0.28	4.82 ± 0.27
Change in hip BMD	3.90 ± 0.23	3.69 ± 0.21	2.78 ± 0.21

* Test for trend: NS.

[†]Test for trend: $p = 0.023$ for associations with changes in spine BMD.

[†]Test for trend: $p = 0.002$ for associations with changes in hip BMD.

All corrected changes significantly greater than zero.

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