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Genetic Effects on Bone Loss in Peri- and Postmenopausal Women: A Longitudinal Twin Study

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ABSTRACT: This longitudinal twin study was designed to assess the heritability of bone loss in peri- and postmenopausal women. A sample of 724 female twins was studied. Baseline and repeat BMD measurements were performed. Results of genetic model-fitting analysis indicated genetic effects on bone loss account for ~40% of the between-individual variation in bone loss at the lumbar spine, forearm, and whole body.

Introduction: BMD and bone loss are important predictors of fracture risk. Although the heritability of peak BMD is well documented, it is not clear whether bone loss is also under genetic regulation. This study was designed to assess the heritability of bone loss in peri- and postmenopausal women.
Materials and Methods: A sample of 724 female twins (177 monozygotic [MZ] and 185 dizygotic [DZ] pairs), 45–82 yr of age, was studied. Each individual had baseline BMD measurements at the lumbar spine, hip, forearm, and total body by DXA and at least one repeat measure, on average 4.9 yr later. Change in BMD (ΔBMD) was expressed as percent of gain or loss per year. Intraclass correlation coefficients for ΔBMD were calculated for MZ and DZ pairs. Genetic model-fitting analysis was conducted to partition the total variance of ΔBMD into three components: genetic (G), common environment (C), and specific environment, including measurement error (E). The index of heritability was estimated as the ratio of genetic variance over total variance.
Results: The mean annual ΔBMD was –0.37 ± 1.43% (SD) per year at the lumbar spine, –0.27 ± 1.32% at the total hip, –0.77 ± 1.66% at the total forearm, –0.36 ± 1.56% at the femoral neck, and –0.16 ± 0.81% at the whole body. Intraclass correlation coefficients were significantly higher in MZ than in DZ twins for all studied parameters, except at the hip sites. Results of genetic model-fitting analysis indicated that the indices of heritability for ΔBMD were 0.38, 0.49, and 0.44 for the lumbar spine, total forearm, and whole body, respectively. However, the genetic effect on ΔBMD at all hip sites was not significant.
Conclusions: These data suggest that, although genetic effects on bone loss with aging are less pronounced than on peak bone mass, they still account for ~40% of the between-individual variation in bone loss for the lumbar spine, total forearm, and whole body in peri- and postmenopausal women. These findings are relevant for studies aimed at identification of genes that are involved in the regulation of bone loss.
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Key words: BMD, bone loss, genetics, twins

INTRODUCTION

Osteoporosis is a common multifactorial disorder of reduced bone mass associated with microarchitectural deterioration of bone tissue leading to bone loss and increased bone fragility. The major consequence of bone loss is fracture. Typical osteoporotic fractures involve the proximal femur, thoraco-lumbar vertebral bodies, and distal forearm, although many bones may be affected.[1–4]

Low BMD is considered the hallmark of osteoporosis. BMD measurements are valuable predictors of the risk of low-trauma fractures.[5] Bone loss is highly variable among individuals, with the typical SD being between 2- and 3-fold higher than the mean rate of loss.[6–8] BMD at any given age is determined by the relative contributions of peak bone mass achieved and subsequent bone loss. It has been suggested that the relative contributions of peak bone mass and bone loss to BMD at 70 yr of age are equal.[9] This implies that BMD in older women is significantly influenced by the rate of bone loss and bone turnover with advancing age. In support of this hypothesis, a cross-sectional twin study specifically selected for older female subjects (mean age, 68 yr) estimated additive genetic effects accounted for 75% of residual variation in spine and hip

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BMD after adjusting for environmental factors including smoking and alcohol intake.[10]

Although the heritability of peak BMD is well documented by family[11–19] and twin[20–26] studies, there is less clear evidence that the variation in bone loss is under genetic regulation.[27] A number of twin studies have attempted to dissect the genetic effect on rate of bone loss.[28–30] However, overall only a few prospective studies on heritability of bone loss have been reported in humans.[17,31–34] No evidence of a genetic contribution to loss of BMD at the midshaft of the radius was found by Christian et al.[31] in 25 monozygotic (MZ) and 21 dizygotic (DZ) older twin men (mean age, 63 yr) followed over a 16-yr period. However, although the length of the study period was sufficient to detect significant bone loss, the sample size was small, and the skeletal site measured is not a typical site of osteoporotic fracture in men or women. Moreover, in a study of older female twins, there was no significant heritability of BMD at the distal forearm, suggesting that environment could be more powerful than genetic effects at this site with aging.[10] Indeed, although the study of Christian et al. found significant within-pair correlations in both identical (MZ) and nonidentical (DZ) twins at the midshaft of the radius (intraclass correlations of 0.62 and 0.48, respectively), bone loss correlated with environmental factors such as smoking and alcohol intake and, after adjustment for these covariates, it was concluded that changes in BMD were more influenced by factors shared within twin pairs rather than genetic factors.[31] There were other limitations to this study apart from the small sample size. Although the period of follow-up was long (16 yr), bone loss at the midshaft site was low (0.45%/yr), with an overall loss of 6.9%, one half the rate reported in postmenopausal women at the same site.[35] In contrast, another small twin study observed genetic influences on change in BMD at the spine and hip in 21 MZ and 19 DZ twin pairs measured over a mean 3-yr period.[33] However, the period of study was relatively short, ranging from only 1–5 yr, the subjects were a mixture of men and premenopausal and postmenopausal women who were largely not losing bone, and the age range was wide, extending from 25 to 65 yr. With regard to longitudinal family studies, a study of 18 extended Mexican families estimated heritability in those 176 subjects >45 yr of age who had serial BMD scans to be 0.39 for the hip, 0.46 for the spine, and 0.45 at the radius.[17]

Thus, there are no current studies in the literature that adequately address the important question of whether the rate of bone loss is heritable at skeletal sites where osteoporotic fractures are common. This study was designed to assess the heritability of bone loss in peri- and postmenopausal women, a population in which bone loss is more readily measured.

MATERIALS AND METHODS

Subjects

Study subjects were female twin pairs with multiple visits, recruited as part of the Sydney Twin Study, which has been running at the Department of Rheumatology of Royal North Shore Hospital, and the Twin and Sisters Study at the Royal Melbourne Hospital. The twins were recruited through the Australian National Health and Medical Research Council (NHMRC) Twin Registry and from local media campaigns. Twins were invited to participate in a study into the genetic and environmental determinants of various diseases including osteoarthritis, cardiovascular disease, asthma, and osteoporosis. The hospitals' Human Research Ethics Committees approved the study. After providing written informed consent, each twin was interviewed separately in accordance with a standard questionnaire to collect demographic, lifestyle, and medical history data, including an assessment of lifetime exercise history, lifelong smoking and alcohol history, and dietary history (including calcium intake).[36] Except for hormone replacement therapy (HRT), twins who used medications or who had medical conditions that could interfere with bone metabolism were excluded from the analysis. HRT use was recorded and included as a covariate in the analyses. HRT use was coded as 0 (never used or use <6 m) or 1 (use ≥6 mo). Zygosity was determined from the twins' self-report using questions from a validated questionnaire.[37] DNA fingerprinting was used to determine zygosity in twin pairs in whom their zygosity was either unknown or disputed.

BMD measurements

Baseline characteristics included age, height (m), weight (kg), BMI (kg/m^2), and menopausal status for women. Whole body, lumbar spine, hip, and forearm DXA scans were performed on Hologic QDR4500W (fan beam) and QDR 1000 (pencil beam) machines (Hologic, Waltham, MA, USA). Twins within each pair were always scanned using the same densitometer. BMD of lumbar spine (L_1–L_4), total hip, forearm, and whole body were obtained from DXA scans using standard protocols as previously described.[38,39] Total forearm BMD was determined as an area weighted mean of the three forearm sites, ultradistal, mid-distal, and one third distal regions of interest (ROI), derived from the standard protocol forearm analysis and also examined individually. Change in BMD (ΔBMD) was expressed as percent gain or loss per year.

Statistical analysis

The resemblance of BMD change within a twin pair was assessed by the intraclass correlation coefficient for MZ and DZ twin pairs separately. In this method, the total variation (about the mean) of a trait was partitioned into two sources: between-pairs (B) and within-pairs (W). The intraclass correlation was estimated as the difference between the two sources over their sum [(B − W)(B + W)]. Under the hypothesis of no genetic effect, it is expected that the correlation coefficient in MZ pairs is the same as in DZ pairs. To test this hypothesis, the modified Fisher's z-transformation procedure[40] was used.

To estimate the heritability (proportion of variance of a trait attributable to genetic factors), we analyzed the data according to the classical twin model.[41] In this model, the variance of a variable trait is partitioned into genetic and

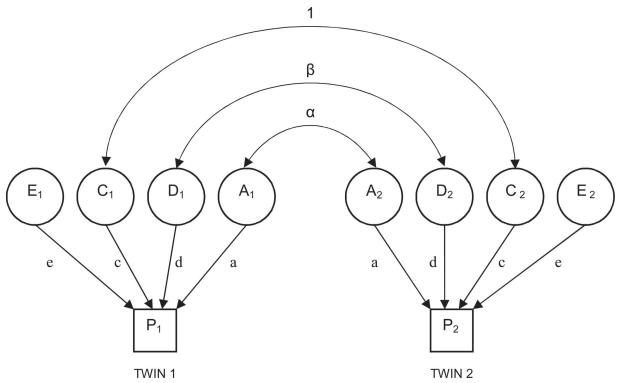

FIG. 1. Path diagram for MZ and DZ twins measured on a single phenotype. Each phenotype (P1, P2) is caused by a linear combination of latent additive genetic (A), dominant genetic (D), common environmental (C), and unique environmental (E) variables. Each latent variable is standardized (i.e., has mean of zero and a variance of one), and the path coefficients of each latent variable on the observed phenotypes are estimated (i.e., a, d, c, e). From biometrical genetics theory, the additive genetic correlation between pairs (a) is 1 for MZ twins and 0.5 for DZ twins. The correlation between dominance variance components (b) is 1 for MZ twins and 0.25 for DZ twins. The correlation between common environmental effects is one for MZ and DZ twins by definition.

environmental components. The genetic variance may be caused by additive (A) or dominant (D) genetic influences. The environmental variance may be caused by environmental factors shared by twins (common environment (C) and to the nonshared environmental factors (E). Shared environmental effects and dominant genetic effects cannot be assessed simultaneously because they are completely confounded in the classical twin models. Additive genetic factors are the effects of genes taken singly and added over multiple loci, whereas dominant genetic factors represent genetic interaction between loci. The classical twin model assumes that additive genetic factors and dominant genetic factors are perfectly correlated in MZ pairs, whereas DZ pairs, like ordinary siblings, share only one half of the additive genetic effects and one quarter of the dominant genetic effects (Fig. 1). The model also assumes that shared environmental effects are perfectly correlated in both MZ and DZ twins; that the effects of assortive mating, epistasis, and the genotype–environmental interaction and/or correlation are negligible; and that shared environmental influences are similar for MZ and DZ twins.

The influences of A, D, C, and E on the phenotype are represented by the parameters a, d, c, and e, respectively, which are equivalent to the standardized regression coefficients (Fig. 1). The amount of variance caused by each source is the square of these parameters. To estimate a, d, c, and e, for each variable trait, the data were summarized into 2×2 variance-covariance matrices. The matrices were subject to analysis specified by five possible models incorporating different combinations of these factors: E, CE, AE, ACE, and ADE. The maximum likelihood method was used to estimate model parameters. Selection of the best model was based on the difference between likelihood ratio χ^2 goodness-of-fit tests. The index of heritability was obtained as the square of the parameter a from the most parsimonious model. In both correlation and heritability analyses, the trait (i.e., BMD change) was adjusted for potential confounders such as age, HRT use (coded as 0 for never use or use <6 mo) or 1 (for use ≥6 mo), smoking, alcohol intake, and physical activity. In the adjusted analysis, the above factors were considered as covariates in the statistical model. In a further separate analysis, all subjects who had ever used HRT for ≥6 mo were excluded.

RESULTS

The characteristics of the 724 peri- and postmenopausal female twins who participated in the study are presented in Tables 1 and 2. There were 177 MZ and 185 DZ pairs. There were no significant differences between MZ and DZ twins in age, baseline BMD, or dietary calcium intake or exercise (data not shown). There were significant differences in height and body mass index, which were adjusted for in the analysis. The age of the twins ranged from 45 to 82 yr at the initial visit (mean age, 56.2 ± 8.0 [SD] yr). The average time between two BMD measurements was 4.9 yr (range, 1–10 yr). At baseline, there were 121 perimenopausal and 603 postmenopausal female twins. Of the 121 perimenopausal women, 86 became postmenopausal during the study. The mean time since menopause ranged from 0 to 35 yr (mean time, 9.4 ± 7.4 yr). During follow-up, the mean percent overall BMD loss was –1.46 ± 4.93 at the lumbar spine, –1.30 ± 4.35 at the total hip, –1.61 ± 4.90 at the femoral neck, –2.98 ± 4.07 at the total forearm, and –0.77 ± 3.34 for the whole body. There was no significant difference in ΔBMD between MZ and DZ twins. Bone loss was greater in twins 40–60 yr of age than those >60 yr of age at most sites (data not shown). The most rapid bone loss was observed for the total forearm (–0.77 ± 1.66%/yr) and the slowest rate of change was present in whole body BMD (–0.16 ± 0.81%/yr). There were no statistically significant differences in the annual rates of loss between the ultradistal, mid-distal, or one-third distal ROIs of the forearm, despite the higher baseline BMD at the one-third distal region (Table 2). ΔBMD was weakly correlated with baseline BMD at most sites (r = –0.140, –0.135, and –0.135 for lumbar spine, femoral neck, and whole body, respectively). There were no statistically significant correlations between baseline BMD and rate of bone loss at the total or regional forearm measurements. Two hundred four women took HRT for between 6 and 12 mo, with 255 women taking HRT for >12 mo. Women taking HRT for >12 mo showed significantly ($p < 0.05$) slower rates of bone loss (–0.89 ± 5.06 at the lumbar spine, –0.42 ± 4.29 at the total hip, –1.13 ± 4.94 at the femoral neck, –2.71 ± 4.82 at the forearm, and –0.37 ± 3.37 at the whole body) compared with those who had never taken it (–1.76 ± 4.31 at the lumbar spine, –1.79 ± 4.31 at the total hip, –1.89 ± 4.87 at the femoral neck, –3.14 ± 3.57 at the forearm, and –0.98 ± 3.30 for the whole body).

The results of intraclass correlation analysis for MZ and DZ twins are presented in Figs. 2A–2C. The correlations

Table 1. Baseline Anthropometric and Lifestyle Characteristics of Twins

	N	*MZ twins (mean ± SD)*	*N*	*DZ twins (mean ± SD)*
Age (yr)	354	56.2 ± 8	370	56.1 ± 8
Time between scans (yr)	354	5.25 ± 2.21	370	4.57 ± 2.24*
Weight (kg)	354	64.88 ± 10.93	370	67.61 ± 12.99*
Height (cm)	354	160.09 ± 6.82	370	160.57 ± 6.25
BMI (kg/m^2)	354	25.35 ± 4.16	370	26.21 ± 4.76*
Menopausal status	53		68	
Perimenopausal	301		302	
Postmenopausal				
Status changed during the study	41		45	
Time since menopause (yr; range)	354	9.50 ± 7.68 (0–28.8)	370	9.37 ± 7.80 (0–35.5)
Hormone replacement therapy				
Never taken or <6 mo	132		133	
Ever taken for ≥6 mo	222		237	

* $p < 0.05$.

Table 2. Baseline BMD Measurements and Rate of Bone Loss

	N	*MZ twins (mean ± SD)*	*N*	*DZ twins (mean ± SD)*
Baseline BMD (g/cm^2)				
Lumbar spine (L_1–L_4)	354	0.98 ± 0.16	370	0.98 ± 0.16
Total hip	352	0.89 ± 0.12	370	0.90 ± 0.14
Femoral neck	352	0.75 ± 0.12	370	0.76 ± 0.12
Total forearm	354	0.53 ± 0.06	369	0.53 ± 0.06
Ulna/radius ultradistal ROI	174	0.54 ± 0.06	188	0.53 ± 0.06
Ulna/radius mid-distal ROI	174	0.57 ± 0.06	188	0.56 ± 0.06
Ulna/radius one-third distal ROI	174	0.66 ± 0.06	188	0.65 ± 0.07
Whole body	352	1.07 ± 0.11	360	1.07 ± 0.12
Average overall change in BMD (%)				
Lumbar spine (L_1–L_4)	354	–1.69 ± 5.11	370	–1.23 ± 4.73
Total hip	352	–1.43 ± 4.68	370	–1.19 ± 4.01
Femoral neck	352	–1.86 ± 5.01	370	–1.38 ± 4.80
Total forearm	347	–3.27 ± 4.65	365	–2.72 ± 3.40
Ulna/radius ultradistal ROI	174	–2.89 ± 3.57	188	–2.38 ± 3.12
Ulna/radius mid-distal ROI	174	–2.85 ± 3.55	188	–2.82 ± 7.80
Ulna/radius one-third distal ROI	174	–2.02 ± 3.97	188	–2.47 ± 7.95
Whole body	324	–0.80 ± 3.59	295	–0.73 ± 3.04
Average annual change in BMD (%/yr)				
Lumbar spine (L_1–L_4)	354	–0.40 ± 1.41	370	–0.35 ± 1.44
Total hip	352	–0.21 ± 1.41	370	–0.33 ± 1.22
Femoral neck	352	–0.38 ± 1.45	370	–0.34 ± 1.67
Total forearm	347	–0.82 ± 2.19	365	–0.72 ± 0.91
Ulna/radius ultradistal ROI	174	–0.66 ± 3.55	188	–0.72 ± 0.97
Ulna/radius mid-distal ROI	174	–0.65 ± 0.81	188	–0.81 ± 1.77
Ulna/radius one-third distal ROI	174	–0.64 ± 0.92	188	–0.70 ± 1.82
Whole body	324	–0.16 ± 0.80	295	–0.17 ± 0.82

* $p < 0.05$.

were higher in MZ pairs than in DZ pairs for all measured parameters, consistent with significant genetic influence on these traits. However, no significant intraclass correlations were found for annual changes in any of the hip BMD measurement sites.

The results of the twin model analyses are presented in Table 3. The maximum likelihood method was used to estimate model parameters. Selection of the best model was based on the difference between likelihood ratio χ^2 goodness-of-fit tests. For lumbar spine, total forearm, and whole body, AE models gave the best fit. The indices of heritability (A) were 38%, 49%, and 44% for annual changes in lumbar spine, total forearm, and whole body ΔBMD, respectively, when all twins were included. The twin analyses

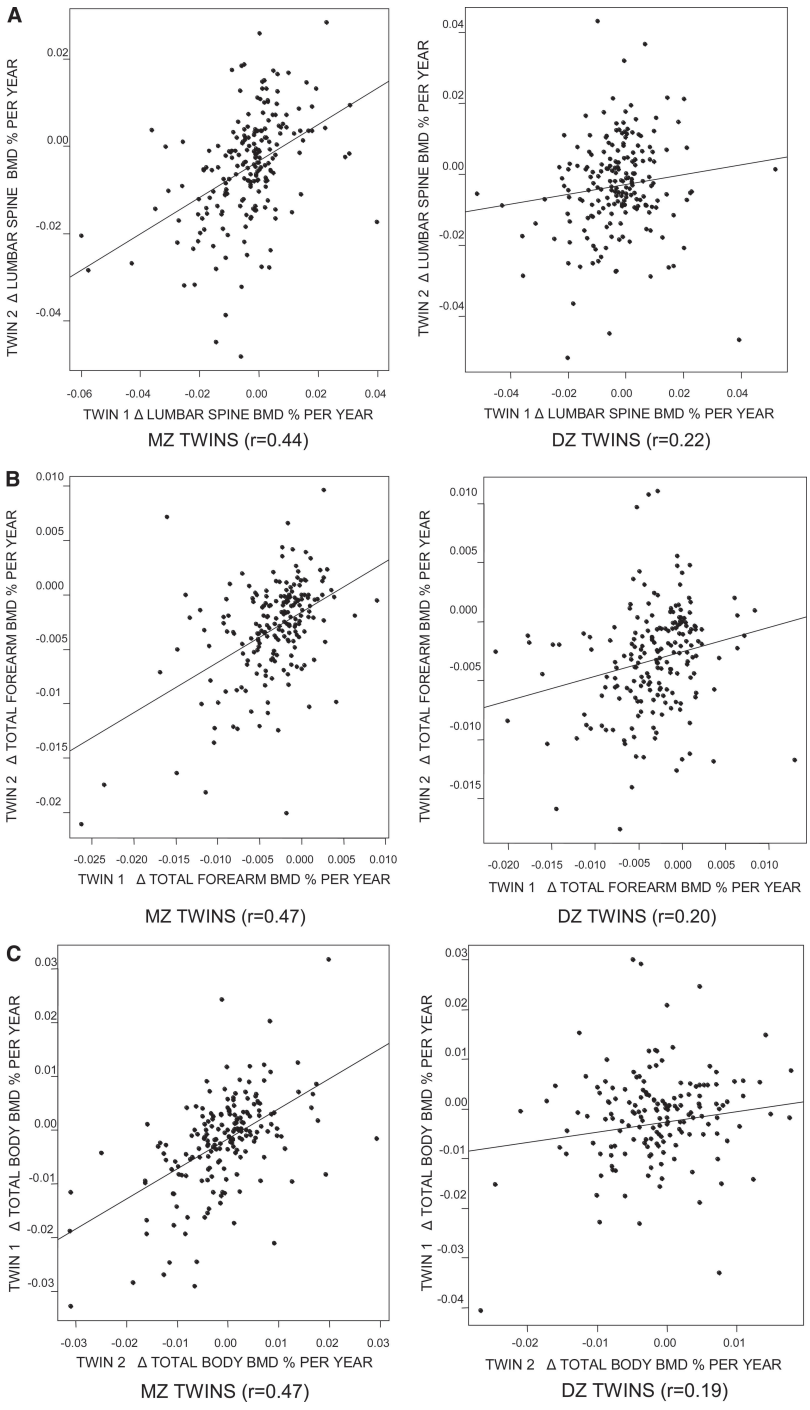

FIG. 2. Intraclass correlations for annual change in (A) lumbar spine BMD, (B) total forearm BMD, and (C) whole body BMD.

of the regional subsites of forearm ΔBMD showed that AE models were also the best fit for all ROIs with indices of heritability (A) of 43%, 75%, and 51% for ultradistal, mid-distal, and one-third distal ROIs, respectively. Adjustment for hormone therapy use by including it as a covariate did not significantly alter these results (Table 3). When HRT users for ≥6 mo were excluded from the analysis, only lumbar spine heritability remained significant, but the power was much reduced at the forearm and whole body sites in this analysis (Table 3).

DISCUSSION

The results of this study suggest that, although genetic effects on bone loss with aging are less pronounced than those on peak bone mass, they account for ~40% of the between-individual variation in bone loss at the lumbar spine, forearm, and whole body in peri- and postmenopausal women.

Susceptibility to osteoporosis is largely genetically determined, and it is likely that many genes are involved, each

TABLE 3. STANDARDIZED PARAMETER ESTIMATES FOR HRT-USER INCLUSIVE AND EXCLUSIVE MODELS

		Not adjusted for HRT		*Adjusted for HRT*	
	Average percent per year	*A estimate (95% CI)*	*E estimate (95% CI)*	*A estimate (95% CI)*	*E estimate (95% CI)*
All twins >45 yr of age including HRT users: 362 twin pairs (177 MZ pairs and 185 DZ pairs)	Lumbar spine	0.384 (0.043–0.551)	0.553 (0.449–0.678)	0.376 (0.036–0.552)	0.551 (0.448–0.675)
	Total forearm	0.487 (0.211–0.584)	0.513 (0.416–0.628)	0.490 (0.188–0.585)	0.510 (0.415–0.626)
	Ulna/radius ultradistal ROI	0.429 (0.128–0.588)	0.571 (0.412–0.766)	0.431 (0.127–0.590)	0.569 (0.410–0.764)
	Ulna/radius mid-distal ROI	0.752 (0.490–0.853)	0.248 (0.147–0.511)	0.754 (0.492–0.854)	0.246 (0.146–0.508)
	Ulna/radius one-third distal ROI	0.506 (0.115–0.748)	0.494 (0.252–0.879)	0.541 (0.153–0.763)	0.459 (0.237–0.845)
	Whole body	0.442 (0.171–0.549)	0.559 (0.451–0.682)	0.447 (0.165–0.553)	0.553 (0.447–0.676)
No HRT users: 186 twin pairs (91 MZ pairs and 95 DZ pairs)	Lumbar spine	0.501 (0.089–0.693)	0.420 (0.308–0.576)		

Values are squared standardized coefficients.

having a small effect.[42] BMD after early adulthood is determined by peak bone mass and subsequent bone loss.[9] Cross-sectional studies in twins[20–23] and families[11–16,18] have shown that peak bone mass is largely influenced by genetic factors. A cross-sectional design, however, cannot directly assess the magnitude of heritability of bone loss. Although BMD may be affected by many genes at different skeletal sites and in different age groups, it is likely that the magnitude of individual genetic effects differs in different populations and in different environmental settings.[22] The San Antonio family osteoporosis study on Mexican-American extended families showed results for heritability of bone loss in the spine and forearm similar to ours, but they also observed significant heritability at the hip.[17] Our study is the first large longitudinal twin genetic epidemiological study to directly quantify the genetic versus environmental components of bone loss variance in peri- and postmenopausal women. Previous twin studies that have measured longitudinal changes in BMD were much smaller studies in men or younger subjects, and the findings were not consistent.[31–33] A longitudinal study of sisters also found a significant genetic influence on change in femoral neck BMD,[34] but the study subjects were premenopausal (mean age, 35.3 yr), and it was unclear whether this effect persisted across the menopause. The reason for these apparent differences between studies at the hip site remains unclear, but greater environmental effects at the hip may decrease the power to show genetic effects at that site.

The benefits of defining the genes causing bone loss and subsequent osteoporotic fractures include identification of individuals who are at greater risk and a better understanding of the disease pathophysiology, which will facilitate the search for novel therapeutic and preventative targets. Whether genetic tests can actually predict those at risk for developing osteoporosis is uncertain. In theory, if all of the genes that cause the disease can be identified, and their interaction with each other and with environmental factors is understood, heritability figures from twin and family studies suggest that this information will be useful in predicting those who are at risk. However, the depth of our knowledge currently falls far short of this goal. Genes that have been implicated, to date, in osteoporosis make only minor contributions individually to BMD and fracture risk, and are not yet of great clinical value. Because osteoporosis is a polygenic disease, predictive tests are likely to involve the typing of several genes, and tests for single genes are less likely to be of clinical significance in most people.

Our study has several strengths and limitations. The mean annual BMD loss in our study was lower than reported in some previous longitudinal studies.[6–8,43–45] However, high rates of bone loss have mainly been observed in the elderly, and our observed rates of loss are similar to other studies of peri- and postmenopausal women.[45–47] Moreover, rates of bone loss may be influenced by multiple factors including age, body composition, and environmental factors. A relative large percentage of our twins had exposure of >6 mo to estrogen therapy, but adjusting for hormone use did not affect the results. More-

over, when the analysis was confined to the twins who had never used HRT, a significant effect of heritability on bone loss was still evident in the lumbar spine. Because baseline BMD is used to calculate rate of loss, bone loss rate can never be truly independent of baseline BMD.[27] Although this phenomenon may account for the observation of faster bone loss in women with higher BMD, the effect of baseline BMD seems to be small.[48] In a reanalysis, controlling for baseline BMD, of 75 women followed for 9.5 yr, Recker at al.[46] estimated that 67% of postmenopausal BMD variation was attributable to premenopausal BMD, whereas 29% was attributable to the bone loss rate. Our figure of ~40% heritability of bone loss would not be inconsistent with that analysis. Our study sample is 10-fold larger than previous longitudinal twin studies and of satisfactory duration (mean 5-yr follow-up), which should diminish the effects of measurement error related to small changes in BMD over time. Inferring a genetic etiology by contrasting MZ and DZ twins rests on the assumption that the twins share a common family environment to the same extent. This assumption may not hold for a number of environmental variables that might affect bone loss such as exercise and smoking.[49] However, the effects of these covariates are likely to be modest.

In conclusion, our data suggest that, although genetic effects on bone loss with aging are less pronounced than on peak bone mass, they account for ~40% of the between-individual variation in bone loss at the lumbar spine, total forearm, and whole body in peri- and postmenopausal women. These findings provide a rational basis for the identification of genes that are involved in the regulation of bone loss.

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