

# Gender Differences in the Genetic Factors Responsible for Variation in Bone Density and Ultrasound

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## ABSTRACT

Although genetic factors are thought to explain a large proportion of the variation in bone density in women, few studies have been conducted in men. Therefore, it is unclear whether the individual differences in bone strength between men and women are a reflection of gender differences in the relative influence of genetic and environmental factors on bone density variance. The aim of this study was to determine if there were gender differences in the genetic components of variance for bone density and ultrasound. In addition, the study aimed to explore the hypothesis that there are unique gender-specific genetic determinants of these traits. Bone mineral density (BMD) of the hip, distal forearm, and lumbar spine were measured by dual-energy X-ray absorptiometry (DXA) as well as quantitative ultrasound (QUS) at the calcaneus in healthy female twin pairs (286 identical [MZ] and 265 nonidentical [DZ]), male twin pairs (72 MZ and 65 DZ), and 82 opposite-sex (OS) pairs aged between 18 and 80 years. For hip BMD, distal forearm, and QUS measurements, the differences between MZ correlations and like-sex DZ correlations were similar for both sexes, suggesting little difference in the component of total variance explained by genetic factors between male and female twin pairs. However, correlations between OS twin pairs were lower than that of like-sex twin pairs, suggesting the possibility of unique gender-specific genetic effects. At the forearm, model fitting suggested a small gender difference in the magnitude of genetic variance as well as the presence of a unique gender-specific genetic variance component. Hip, lumbar spine, and QUS measurements were better explained by models that assumed no gender differences in genetic variance between the sexes, but the study had insufficient power to detect small differences in the genetic components of variance. The results of this study suggest that the proportion of bone strength variance explained by genetic factors is similar for men and women. However, at some regions there is evidence to suggest a gender-specific genetic component to the overall genetic variance. (*J Bone Miner Res* 2002;17:725–733)

**Key words:** osteoporosis, bone density, gender, genetics, twins

## INTRODUCTION

**I**MPORTANT DIFFERENCES in the epidemiology of osteoporosis between men and women may be an indicator of gender differences in the genetic factors responsible for the

variation in bone strength. There are notable differences in the incidence of osteoporotic fractures between the two sexes.<sup>(1,2)</sup> When osteoporosis is defined by gender-specific bone mineral density (BMD) cut-offs (World Health Organization [WHO] definition, BMD > 2.5 SD below the young normal mean), there are differences in the prevalence of osteoporosis between men and women.<sup>(3,4)</sup> A number of

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studies have shown that for women, there is significantly higher bone loss in the immediate postmenopausal period<sup>(5-7)</sup> compared with men of the same age. Moreover, longitudinal studies that have directly compared bone loss between older men and women also have shown consistently higher rates of bone loss in women than men even as old as 85 years.<sup>(8-10)</sup> In addition, gender differences have been reported in iliac crest bone samples between sexes.<sup>(11)</sup>

Usually, bone strength is assessed by measurement of BMD, whereas quantitative ultrasound (QUS) is thought to reflect the structural properties of bone. Twin and family studies have shown that genetic factors have the largest influence on the individual variation in these traits (heritability, 50–80%).<sup>(12-19)</sup> However, most of these studies were on female twins, so it is unknown if the magnitude of the genetic components of variance for bone strength and quality are the same for both genders and whether it is the same set of genes responsible for the individual variation in bone strength in both men and women.

Twin studies have an advantage over family studies in that they are not confounded by age and cohort effects and can separate common environment from genetic effects. The inclusion of opposite sex (OS) twins in the twin design has the added benefit of allowing estimations of gender-specific genetic components of variance. Therefore, the aim of this study was to determine if there were any gender differences in the magnitude of genetic variances for BMD and ultrasound. In addition, the study aimed to explore the hypothesis that there are unique gender-specific genetic determinants for these traits using the OS twin model.

## MATERIALS AND METHODS

### *Subjects*

The study cohort consisted of like-sex, identical (MZ) and nonidentical (DZ) twin pairs, as well as OS twin pairs. 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 an investigation into the genetics of various diseases including osteoarthritis, cardiovascular disease, asthma, and osteoporosis. The hospitals' Human Research Ethics Committee approved the study.

Each twin was interviewed separately using a structured questionnaire to obtain information on demographic details and risk factors for osteoporosis. Twins who used medications or who had medical conditions that could interfere with bone metabolism were excluded from the analysis.

Zygosity in like-sex twins was determined from the twins' self-report using questions from a validated questionnaire.<sup>(20)</sup> DNA fingerprinting was used to determine zygosity in twin pairs in which their zygosity was either unknown or disputed.

### *Measurement of BMD and QUS*

BMD at the left hip, forearm, and lumbar spine (L1–L4) was measured on the same dual-energy X-ray absorptiometry (DXA) machine (QDR 4500; Hologic, Inc., Waltham,

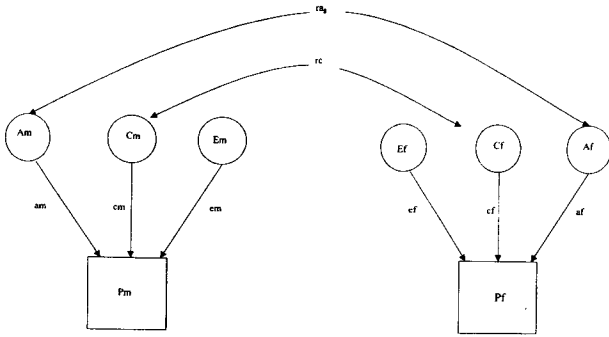
MA, USA). BMD measurements were obtained from two regions of the proximal femur: total hip and neck of femur (NOF). QUS parameters were measured on the same day at the left calcaneus using a McCue Cuba Mark II (McCue Ultrasonics, London, UK) to obtain broadband ultrasound attenuation (BUA) and velocity of sound (VOS). The operator was "blind" to the BMD results.

### *Statistical analysis*

MZ twin pairs share identical genotypes; therefore, any differences between them are caused by their environments. DZ twins (like-sex and OS pairs) in contrast are no more alike genetically than siblings, sharing on average 50% of their genes. In classic twin analysis, it is assumed that both types of twins share the same common environmental influences so the extent to which MZ twin pairs are more alike for a trait than DZ sex twin pairs reflects the degree of genetic influence on the population variance of that trait. In the classic twin method, this can be determined by comparing the intraclass correlation coefficients calculated in the twin groups separately.<sup>(21)</sup> The association between BMD and QUS parameters and a number of possible predictors such as age, age<sup>2</sup>, weight, height, and hormone-replacement therapy (HRT) use were determined first by multiple regression analysis using methods described previously, which take account of the correlation of estimated error terms of regression parameters within twin pairs.<sup>(22)</sup> Then, intraclass correlations were calculated in MZ, DZ (male and female), and OS pairs using the residuals produced from the regressions. Differences in the correlation between MZ and like-sex DZ twin pairs were compared to give an indication of whether the proportion of BMD and ultrasound variance explained by genetic factors was the same for men and women. Then, like-sex DZ correlations were compared with OS pair correlations to see if there were any qualitative genetic differences between the sexes. If OS pairs share  $1 < 50\%$  of the genes influencing the variance of the trait of interest (compared with 50% in like-sex DZ pairs), then correlations in OS pairs would be lower than in DZ pairs, suggesting the presence of gender-specific effects. The test of significance of correlation differences between twin groups was based on the modified Fisher's z-transformation procedure.<sup>(23)</sup>

Estimates of genetic and environmental effects based on comparison of intraclass correlations have limitations; therefore, genetic model-fitting techniques also were used to provide quantification of the variances. The data from this study was analyzed by twin path analysis as detailed elsewhere.<sup>(24-27)</sup>

Using path analysis it was possible to quantify the relative influence of genetic and environmental effects on total phenotypic variance. Genetic variance itself may be caused by additive (A) or dominant (D) genetic components. The A genetic factors are the effects of genes taken singly and added over multiple loci, whereas D genetic factors represent genetic interaction within loci. The environmental variance may be caused by common (shared) environmental factors (C) shared by both twins and to nonshared environmental factors (E) that include any measurement error. In



**FIG. 1.** General sex-limitation model. Path diagram is shown for OS pair twins. Observed variables for twin 1 and twin 2 are shown in the squares. Latent variables (or factors) are shown in circles. A single-headed arrow indicates a direct influence of one variable on another, its value represented by a path coefficient. Double-headed arrows indicate a correlation without any assumed direct relationship. *m*, = male; *f*, female; *A*, additive genetic factor; *C*, common environmental factor; *E*, unique environmental factor; *Pm* (*Pf*), phenotypic value of male and female twins; *a*, additive genetic factor loading; *c*, common environmental factor loading; *e*, unique environmental factor loading;  $ra_g$ , additive genetic correlation;  $rc$ , common environment correlation;  $ra_g = 1$  for MZ and 0.5 for like-sex DZ twins;  $rc = 1$  for MZ and like-sex DZ twins. In the analysis, the data are fitted to six different models by varying assumptions for OS pairs:

- Model I:  $am \neq af, cm \neq cf, em \neq ef$  - estimate  $ra_g$  - fix  $rc = 1$   
 Model II:  $am \neq af, cm \neq cf, em \neq ef$  - fix  $ra_g = 0.5$  - estimate  $rc$   
 Model III:  $am \neq af, cm \neq cf, em \neq ef$  - fix  $ra_g = 0.5$  - fix  $rc = 1$   
 Model IV:  $am = af, cm = cf, em = ef$  - estimate  $ra_g$  - fix  $rc = 1$   
 Model V:  $am = af, cm = cf, em = ef$  - fix  $ra_g = 0.5$  - estimate  $rc$   
 Model VI:  $am = af, cm = cf, em = ef$  - fix  $ra_g = 0.5$  - fix  $rc = 1$

this method of analysis, a test of goodness of fit of the model is determined, which allows comparisons of alternative models. Figure 1 shows a more complex variation on the classical twin model that allows for gender differences in the genetic and E factor effects on trait variance. The model shown is for the OS twin pairs although in the analysis, all twin groups were analyzed simultaneously. A limitation of classic twin analysis is that shared E factors and D genetic factors cannot be included in the one model, because these two factors are heavily confounded and cannot be distinguished from each other. An ACE model was assumed for all the traits, so that submodels with gender differences in genetic and shared E effects could be tested. The influences of A, C, and E on trait variance are represented by the parameters  $am$ ,  $cm$ , and  $em$  for men and  $af$ ,  $cf$ , and  $ef$  for women, respectively. These parameters are equivalent to the standard regression coefficients and the variance because each source is the square of these parameters. To include the possibility of unique gender-specific factors, the correlation of genetic factors between the men and women in the OS pairs ( $ra_g$ ) can be estimated. If  $ra_g$  is found to be significantly  $<0.5$  in the OS pairs, it implies the presence of a unique gender-specific genetic component. In the classic twin model, the correlation of C effects is assumed to be 1.0 within twin pairs reared together for both MZ and like-sex DZ pairs. This may not be the case for the OS-DZ pairs. To account for the possibility that OS pairs share environment

to a lesser extent, the correlation of C factors between men and women in the OS pairs ( $rc$ ) can be estimated also.

A number of different models (models I–VI) were compared to see which model best explained the data (Fig. 1). By comparing models in which A, C, and E effects are the same ( $am = af, cm = cf, em = ef$ ) with models in which they are different between the sexes and by either allowing flexible parameterization of  $ra_g$  or fixing them at 0.5 and 1.0, respectively, analogous to the like-sex DZ groups, it was possible to “test” a number of explanations for the observed covariances for BMD and ultrasound between twin pairs. These included the possibility of unique gender-specific genetic effects, gender differences in magnitude of genetic effects, less sharing of C effects in OS pairs, and no difference in genetic or environmental factors between the sexes. In deciding the model with the best fit, submodels were compared with the full models by hierarchical  $\chi^2$  tests and the decision also was guided by the minimum value of the Akaike Information Criterion, which is equal to  $X^2 - 2$  degrees of freedom (df).

The magnitude of A, C, and E components of variance were expressed as a standardized ratio of  $a^2$ ,  $c^2$ , and  $e^2$ , respectively, over total phenotypic variance.

Data handling and preliminary analyses were done using STATA (Stata Corp., College Station, TX, USA) and quantitative genetic modeling was performed with Mx, the software package (Commonwealth University of Virginia, Richmond, VA, USA).<sup>(28)</sup>

## RESULTS

Two hundred eighty-six female MZ, 265 female DZ, 72 male MZ, 65 male DZ, and 82 OS twin pairs were seen (Table 1). There was no significant difference in mean age between any of the groups. Weight, height, and body mass index (BMI) were higher in men than in women. For both sexes, the mean weight and BMI was highest in the OS groups and then the DZ groups. Some differences in mean BMD and QUS values also were seen between same-sex groups but these differences were not significant after adjustment for age, age<sup>2</sup>, weight, height, and sex (data not shown). In addition, variances for BMD and QUS parameters were not different between the twin groups.

The correlations were higher in MZ pairs than in DZ pairs for all measurements, consistent with significant genetic influence on the variation of these traits in both sexes (Table 2). The correlations also suggest that the magnitude of genetic variance is the same for both sexes, because the differences in correlation between MZ pairs and DZ pairs were similar for women and men for all traits except for the lumbar spine. Compared with the like-sex DZ groups, the correlations in the OS group were generally lower, raising the possibility of gender-specific genetic determinants. The largest differences in correlation between these two groups were seen at forearm, lumbar spine, and BUA but did not reach statistical significance.

The results of the model-fitting analysis for NOF BMD and forearm BMD are summarized in Tables 3 and 4, respectively. NOF BMD was best explained by the model

TABLE 1. CHARACTERISTICS OF TWIN STUDY POPULATION CATEGORIZED BY SEX AND TWIN ZYGOSITY

	Female MZ (n = 574)	Female DZ (n = 530)	Female OZ (n = 82)	Male MZ (n = 144)	Male DZ (n = 130)	Male OZ (n = 82)
Mean age	48.7	48.3	48.7	49.8	49.4	48.7
(SD)	(15.8)	(13.5)	(13.6)	(14.4)	(16.2)	(13.6)
Mean weight (kg)	64.5	67.3	69.7	81.8	81.8	85.9
(SD)	(11.4)	(12.8)	(14.6)	(11.7)	(14.0)	(15.3)
Mean height (cm)	160.9	162.6	162.5	174.1	174.5	175.9
(SD)	(6.4)	(6.5)	(7.0)	(6.0)	(7.2)	(6.5)
Mean BMI (kg/m <sup>2</sup> )	25.0	25.5	26.4	27.0	26.8	27.7
(SD)	(4.5)	(4.9)	(5.3)	(3.5)	(3.6)	(4.3)
% Postmenopausal	51%	51%	50%			
HRT use	20%	22%	22%			
Total hip BMD (g/cm <sup>2</sup> )	0.89	0.93	0.94	1.04	1.06	1.07
(SD)	(0.12)	(0.13)	(0.13)	(0.12)	(0.13)	(0.14)
NOF BMD (g/cm <sup>2</sup> )	0.77	0.79	0.81	0.86	0.87	0.89
(SD)	(0.12)	(0.13)	(0.12)	(0.12)	(0.13)	(0.12)
Forearm BMD (g/cm <sup>2</sup> )	0.54	0.55	0.55	0.65	0.65	0.67
(SD)	(0.06)	(0.06)	(0.06)	(0.05)	(0.07)	(0.06)
Lumbar BMD (g/cm <sup>2</sup> )	0.97	0.99	1.00	1.03	1.05	1.05
(SD)	(0.14)	(0.15)	(0.13)	(0.11)	(0.16)	(0.14)
BUA (db MHz <sup>-1</sup> )	81.3	81.5	84.6	95.7	90.6	96.2
(SD)	(18.9)	(18.0)	(18.9)	(18.0)	(18.3)	(17.3)
VOS (ms <sup>-1</sup> )	1652	1654	1653	1659	1655	1655
(SD)	(45)	(44)	(42)	(37)	(44)	(42)

TABLE 2. INTRACLASS CORRELATION COEFFICIENTS FOR BMD AND QUS PARAMETERS (ADJUSTED FOR AGE, AGE<sup>2</sup>, WEIGHT, HEIGHT, AND SEX)

Variable	Intraclass correlation (95% CI)				
	Female MZ (286 pairs)	Female DZ (265 pairs)	Male MZ (71 pairs)	Male DZ (65 pairs)	Male-female OZ (82 pairs)
Total hip BMD	0.80 (0.75–0.84)	0.38 (0.27–0.48)	0.82 (0.73–0.89)	0.28 (0.03–0.49)	0.28 (0.07–0.47)
NOF BMD	0.83 (0.79–0.86)	0.27 (0.15–0.38)	0.78 (0.67–0.86)	0.44 (0.22–0.62)	0.32 (0.11–0.50)
Forearm BMD	0.78 (0.73–0.82)	0.40 (0.30–0.50)	0.87 (0.79–0.92)	0.40 (0.18–0.59)	0.19 (–0.03–0.39)
Lumbar BMD	0.70 (0.64–0.76)	0.38 (0.27–0.48)	0.78 (0.66–0.86)	0.56 (0.37–0.71)	0.17 (–0.05–0.37)
BUA	0.62 (0.54–0.68)	0.36 (0.25–0.46)	0.64 (0.48–0.76)	0.18 (–0.07–0.40)	0.16 (–0.06–0.37)
VOS	0.76 (0.71–0.81)	0.40 (0.30–0.50)	0.64 (0.47–0.76)	0.28 (0.04–0.49)	0.37 (0.16–0.54)

that assumed no gender difference in the magnitude of genetic variance and no gender-specific genetic effects (Table 3, model VI based on the model selection criteria mentioned previously). However, at the forearm the data were best explained by model I (Table 4), which assumed differences in the effects of A, C, and E between the sexes and gender-specific effects ( $r_g < 0.5$ ; i.e., a gender-specific genetic component of variance for BMD). However, it is important to note that it was not always easy to discriminate between models based on best fit. For example, in Table 3, model IV, which assumes gender-specific effects ( $r_g =$

0.36) for NOF BMD, has similar fit statistics to model VI, which was regarded as the best-fitting model.

Model fitting for lumbar spine (data not shown) used data on twins aged <50 years because all models fitted poorly (reflected by the fit statistics) when the older twins were included in the analysis. This was thought to be caused by the confounding effect of osteoarthritis of the spine on BMD measurements in the older twins. Model VI, which assumed no gender differences, fitted the data best, but model IV, which assumed gender-specific effects, had similar fit statistics. QUS parameters were best explained also

TABLE 3. STANDARDIZED PARAMETER ESTIMATES AND MODEL FIT STATISTICS FOR NOF BMD

Model number <sup>a</sup>	Model estimates and fixed assumptions			Squared standardized coefficients						Fit statistics			
	Male = Female for values of A, C, and E (Yes or No)	Genetic correlation (r <sub>g</sub> ) (95% CI)	Common environment correlation (r <sub>c</sub> ) (95% CI)	A estimate (95% CI)		C Estimate (95% CI)		E Estimate (95% CI)		df	X <sup>2</sup>	p Value	AIC
				A estimate (95% CI)	C Estimate (95% CI)	E Estimate (95% CI)	E Estimate (95% CI)						
I	No	0.38 (0.12-0.71)	Fixed	0.78 (0.45-0.88) M	0.04 (-0.36-0.36) M	0.18 (0.12-0.26) M	8	14.7	0.07	-1.30			
II	No	Fixed	1.0	0.85 (0.79-0.88) F	0.0 (-0.06-0.06) F	0.15 (0.12-0.18) F	8	15.4	0.05	-0.59			
III	No	0.5	-1.0-1.0	0.70 (0.43-0.87) M	0.12 (-0.38-0.38) M	0.12 (0.12-0.26) M	9	15.4	0.08	-2.59			
IV	Yes	Fixed	Fixed	0.85 (0.78-0.88) F	0.0 (-0.07-0.07) F	0.15 (0.12-0.18) F	11	16.0	0.1	-6.01			
V	Yes	0.36 (0.13-0.55)	1.0	0.70 (0.43-0.87) M	0.12 (-0.38-0.38) M	0.18 (0.12-0.26) M	11	17.8	0.1	-4.18			
VI	Yes	Fixed	-1.0-1.0	0.85 (0.75-0.87)	0.0 (-0.09-0.09)	0.15 (0.13-0.18)	12	17.8	0.1	-6.18			
		0.5	Fixed	0.85 (0.79-0.87)	0.0 (-0.05-0.05)	0.15 (0.13-0.18)							
		Fixed	1.0										

<sup>a</sup> See Fig. 1. AIC, Akaike's information criterion; M, male; F, female.

TABLE 4. STANDARDIZED PARAMETER ESTIMATES AND MODEL FIT STATISTICS FOR FOREARM BMD

Model number <sup>a</sup>	Model estimates or fixed assumptions			Squared standardized coefficients						Fit statistics		
	Male = Female for values of A, C, and E (Yes or No)	Genetic correlation ( $r_{g_e}$ ) (95%CI)	Common environment correlation ( $r_c$ ) (95% CI)	A estimate (95% CI)	C estimate (95% CI)	E estimate (95% CI)	E estimate (95% CI)	df	X <sup>2</sup>	P Value	AIC	
I	No	0.21 (-0.11-0.60)	Fixed	0.89 (0.65-0.92) M	0.0 (-0.23-0.23) M	0.11 (0.08-0.17) M	0.11 (0.08-0.17) M	8	3.7	0.9	-12.3	
II	No	Fixed	1.0	0.74 (0.55-0.82) F	0.04 (-0.22-0.22) F	0.22 (0.18-0.26) F	0.22 (0.18-0.26) F	8	6.1	0.6	-9.9	
III	No	0.5 Fixed	(-0.05-1.0)	0.67 (0.52-0.79) F	0.11 (0.03-0.26) F	0.22 (0.18-0.27) F	0.22 (0.18-0.27) F	9	10.0	0.3	-8.0	
IV	Yes	0.19 Fixed	1.0	0.89 (0.83-0.92) M	0.0 (0.0-0.4) M	0.11 (0.08-0.17) M	0.11 (0.08-0.17) M	11	28.4	0.0	6.4	
V	Yes	(-0.1-0.40) Fixed	-1.0-1.0	0.66 (0.49-0.81) F	0.12 (-0.32-0.28) F	0.22 (0.19-0.27) F	0.22 (0.19-0.27) F	11	38.1	0.0	16.1	
VI	Yes	0.5 Fixed	1.0	0.81 (0.64-0.84)	0.0 (-0.17-0.17)	0.19 (0.16-0.22)	0.19 (0.16-0.22)	12	38.1	0.01	14.1	

<sup>a</sup>See Fig. 1.  
AIC, Akaike's information criterion; M, male; F, female.

by model VI, but two models assuming gender differences (models III and IV) were a poorer explanation of the data, but not by much (data not shown).

An alternate hypothesis for the lower correlation in OS pairs compared with like-sex DZ pairs is that OS pairs share environments to a lesser degree. Models that allowed flexible parameterization of common environment correlation ( $rc$ ) generally found the same model fit statistics and A, C, and E values for the range of  $rc$  values from  $-1$  to  $1$ . In the models in which one of the common environment components was zero, it was not possible to define  $rc$  to a point estimate using these statistical techniques.

## DISCUSSION

Gender differences in BMD and bone ultrasound are well documented. However, it is unclear whether this reflects differences between men and women in the genetic and environmental factors responsible for the variance of these traits. The results of this study would suggest that the proportion of BMD and bone quality variance explained by genetic factors is the same in men and women. By including OS twins, it was possible to look for unique gender-specific genetic effects. The results of the study suggest this may be present at the forearm but not to the same degree at the hip, lumbar spine, or calcaneus.

Few studies have attempted to look for gender differences in the relative influence of genetic and environmental factors on bone strength variance. A cross-sectional analysis on unrelated elderly men and women found that the total percentage of BMD variance explained by environmental risk factors was higher in women (17.3–24.5%) than in men (4.7–17.7%).<sup>(29)</sup> No previous twin study has compared directly the genetic factors responsible for bone density variance between men and women. The majority of twin studies that measured BMD have only studied female twins. Male twins were examined in small early studies when like-sex male and female twins were pooled together.<sup>(17,30,31)</sup> The largest male twin study<sup>(32–34)</sup> looked at bone mass at the midshaft of the radius only. A statistically significant genetic influence on baseline radial bone mass variance was found (heritability 0.36 in men aged 44–54 years)<sup>(32)</sup> but diminished 16 years later.<sup>(33)</sup> Comparison between these studies and recent female twin studies is difficult because the instruments to measure forearm BMD have changed over time.<sup>(13–15)</sup> There are no studies in male twins on the heritability of BMD variance at other regions (e.g., spine and hip) or on the heritability of other measures of bone strength in men. The results of our study would suggest that genetic variances are of a similar value for bone density and bone quality in men and women. It follows that the proportion of population variance explained by environmental factors also is likely to be similar.

The most interesting finding of this study is the possibility of gender-specific genetic effects on the variation in bone density. The lower correlations in the OS twin pairs for all traits compared with the like-sex DZ pairs suggest the possibility of unique gender-specific genetic factors. The model-fitting analysis found this significant at the forearm.

The finding that gender-specific genetic factors were only significant at some sites may reflect different structural properties of bone between these sites. The distal forearm, for example, has a higher proportion of trabecular bone than the proximal hip. Within the QUS measurements, the correlation among the OS pairs was lower for BUA ( $r = 0.19$ ) than for VOS ( $r = 0.45$ ), which might be explained by the fact that they are measuring different aspects of bone structure.<sup>(35)</sup>

In theory, it is possible that there are specific genes involved in osteoporosis that exist only in men or only in women, but for this to be the case, they would have to be located on the sex chromosomes. A more likely explanation is that the effects of genes responsible for variation in BMD and QUS are different between the sexes. Hormonal differences between the sexes could account for such different gene expressions. Molecular genetic studies show evidence of a link between sex hormones and genes associated with BMD, for example, the estrogen receptor gene.<sup>(36)</sup> Gender differences in gene expression also could result from other modifying factors (e.g., environmental factors like calcium intake resulting in differences in gene-environment interactions between the sexes). Furthermore, it is realistic to expect that genotyping might one day find gender-specific effects in osteoporosis, because recent studies investigating the effects of gene polymorphism in other diseases have shown gender-specific effects.<sup>(37–39)</sup>

The main strength of this study is that unique to genetic epidemiological studies in this field, a large number of men, women, and OS twin pairs were recruited from the same population base and investigated by the same study methods. Moreover, the conclusions were based on a number of different variables measured at multiple sites.

However, the present findings must be interpreted in the context of a number of possible limitations. The data were obtained from a white population in Australia, among whom cultural backgrounds and environmental living conditions generally are homogenous. Therefore, care should be taken in extrapolating these results to nonwhite populations. Importantly, these data were obtained from twins who are not necessarily representative of the general unrelated population. However, the variances of bone density and QUS in this twin sample are comparable with those observed in unrelated populations. Moreover, a recent study found little difference in BMD and lifestyle characteristics between twin participants from a twin registry for a study of diseases of aging and a parallel population-based study of singleton women.<sup>(40)</sup> It has been argued that MZ twins are likely to share more similar environments than DZ pairs, leading to an overestimation of genetic effects.<sup>(41)</sup> Although the shared environment (C) did not seem to be significant in most of the traits measured, the classic twin model generally has little statistical power to detect these shared environmental effects.<sup>(42)</sup> Partly as a result of this, the analysis by genetic modeling is not able to explore fully the possibility that the lesser sharing of the genetic effect in OS twin pairs could be confounded by lesser environmental sharing in the same group. Finally, the cross-sectional nature of this study does not account for the fact that the genetic and environmental influences may change over time. There is evidence

that the common environmental effects on BMD variance peak during adolescence<sup>(1,3)</sup> and it is plausible that the lower correlation in male-female adult twins is the result of gender differences in shared environmental effects occurring earlier in life.

Despite the large number of twin pairs seen in comparison with previous twin studies, there are a number of limitations related to the power of the study. A larger number of female twins than male twins were recruited in this study. This discrepancy is unlikely to have affected the main results from the twin pair correlations. However, it may have influenced the model-fitting analysis, both in terms of the type of models found to be of best fit and in terms of the model-fitting parameters. In addition, the correlation results would suggest that with larger numbers, the conclusion that genetic variances were the same in magnitude between the sexes would still hold. However, with more OS twin pairs, the differences between this group and the like-sex DZ pairs may have become statistically significant, implying significant gender-specific genetic effects at these sites. Power calculations for the model-fitting analysis suggest that with the number of twin pairs seen, this study had ~80% power at the 0.05 level to detect a difference in genetic contribution (heritability) of 20% between men and women and similar power to detect a <25% sharing of genetic factors (genetic correlation < 0.125) between men and women. More OS twin pairs would have had to be seen to detect more subtle differences in genetic variances between the sexes. For instance given the same number of like-sex twin pairs, you would need >500 OS twin pairs to show that a 75% sharing of genetic influences (genetic correlation = 0.375) represented a significant gender difference.

To conclude, this twin study has shown that the role of genetic factors in determining the population variance of bone mass and structural properties of bone among men and among women is similar. Although the magnitude of this genetic effect may be similar between the sexes, there was some evidence to suggest differences in the set of genes influencing these traits (i.e., gender-specific genetic effects).

The findings from this study about gender differences and similarities in the genetic determinants of osteoporosis are important for a number of reasons. The fact that the absolute magnitude of the genetic contribution to bone strength variance is the same in men and women suggests little differences in the contribution of environmental risk factors as a whole. Therefore, preventative strategies based on environmental risk factor modification theoretically are likely to be equally effective in men and women. The possibility that there are some differences in the genes for bone density between men and women has implications for current and future genetic research into osteoporosis. Currently, a number of groups worldwide are undertaking candidate gene and genomewide linkage analyses using family data on bone density. All of these analytical approaches are limited in their statistical power to detect genetic effects. Their power would be enhanced substantially if it were shown valid to pool data from men and women. Our study, by raising the possibility of the expression of different genes in men and women at some sites, would question the validity

of this. For example, there may be a need to replicate findings on men and women separately at the forearm while it may be valid to pool hip BMD data. Further molecular genetic studies will need to be conducted before the nature of any gender-specific genes for osteoporosis can be answered. Until then, we should more seriously address the issue of gender in the planning and interpretation of studies of osteoporosis.

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