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Muscle cross-sectional area and structural bone strength share genetic and environmental effects in older women

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CONFLICT OF INTEREST

All authors have no conflicts of interest.

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ABSTRACT
The purpose of this study was to estimate to what extent muscle cross-sectional area of the lower leg (mCSA) and tibial structural strength are influenced by common and trait-specific genetic and environmental factors. Peripheral quantitative computed tomography scans were obtained from both members of 102 monozygotic (MZ) and 113 dizygotic (DZ) 63- to 76-year-old female twin pairs to estimate the mCSA of the lower leg, structural bending strength of the tibial shaft (BSIbend) and compressive strength of the distal tibia (BSIcomp). Quantitative genetic models were used to decompose the phenotypic variances into common and trait-specific additive genetic (A), shared environmental (C) and individual environmental (E) effects. The age-adjusted trivariate independent pathway model showed that the total relative contributions of A, C and E were, respectively, 75%, 0% and 25% for mCSA, 55%, 20% and 25% for BSIbend and 40%, 37% and 23% for BSIcomp. In addition, the model showed that all three traits shared genetic and individual environmental factors. BSIbend and BSIcomp had common shared environmental factors and were also influenced by trait-specific genetic factors. In conclusion, the association between muscle cross-sectional area and structural bone strength has its origins in both genetic and environmental effects in older women. These results suggest that in older women the same genetic and environmental factors may predispose to or, conversely, protect from both sarcopenia and bone fragility.

Key words: heritability, bone strength, muscle, aging, osteoporosis
INTRODUCTION

With aging the human musculoskeletal system undergoes changes, which gradually impair its functionality. Skeletal muscle mass is substantially lower in older than in young people\(^{(1)}\) and this is accompanied by large differences in skeletal muscle strength.\(^{(2)}\) This phenomenon of loss of skeletal muscle mass and consequent decline in muscle strength with aging is known as sarcopenia.\(^{(3)}\) Decreased strength of the lower limbs may result in mobility limitations,\(^{(4, 5)}\) a risk factor for falling.\(^{(6)}\) Falls are, in turn, a major risk factor for fractures.\(^{(7)}\) Also the skeleton loses its mass, and the geometry of bones changes with aging.\(^{(8, 9)}\) These changes make the skeleton more susceptible to osteoporotic fractures.\(^{(10)}\) The inevitable impairments in muscle and bone make both sarcopenia and osteoporosis common conditions in older people.\(^{(3, 11)}\)

It has been suggested that sarcopenia and osteoporosis co-exist,\(^{(12)}\) and they may also share a common etiology. This co-existence could further increase the risk for fractures and disability. Indicators of sarcopenia and osteoporosis, i.e. muscle mass and bone traits, have been found to correlate in several studies.\(^{(13-17)}\) For example, DXA-based studies have shown that lean tissue mass, a surrogate for muscle mass, correlates with areal bone mineral density (aBMD, g/cm\(^2\)) and bone mineral content (BMC, g).\(^{(13, 18)}\) However, since aBMD fuses the information on volumetric bone mineral density and bone geometry,\(^{(19)}\) it is not possible to separate which bone trait is truly associated with muscle using DXA. Actually, QCT studies have shown that rather than volumetric bone mineral density bone cross-sectional area is associated with muscle cross-sectional area.\(^{(15, 20)}\) Also, muscle volume and estimated torque produced by muscles have been found to explain differences in structural bone strength.\(^{(16, 21, 22)}\) The association observed between muscle and bone has often been argued to be merely a result of the forces that muscles exert on the bones.\(^{(23)}\) However, some of this association between the traits may be attributable to common genes regulating both tissues\(^{(24-26)}\) but this issue has received less attention.
Karasik and Kiel\(^{(12)}\) highlighted recently the importance of investigating the biological associations between sarcopenia and bone fragility. They stated particularly the need for studies using bone structure rather than aBMD as an outcome. In this respect, peripheral quantitative computed tomography (pQCT) provides useful information on bone geometry, volumetric density and the distribution of bone mineral within a given cross-section.\(^{(27)}\) This structural information is relevant for estimating bone strength at bone sites which are subjected to specific habitual mechanical demands. For example, the tibial shaft needs to have resistance against muscle-induced bending forces whereas the distal tibia mainly bears compressive loads from locomotive reaction forces. The purpose of this study was to estimate the relative contribution of genetic and environmental effects to individual differences in pQCT-derived cross-sectional area of the lower leg muscles and structural bending and compressive strength indices of the tibia among older women and also to investigate to what extent these bone and muscle traits share genetic and environmental effects.
MATERIALS AND METHODS

Subjects

The present study is a part of the Finnish Twin Study on Aging (FITSA), a study on the genetic and environmental influences on the disablement process in older women. The participants were recruited from the nationwide Finnish Twin Cohort which comprises all same-sex twin pairs born before 1958 and with both co-twins alive in 1975. An invitation to participate in the study was sent to 414 female twin pairs aged 63-76 years on the basis of age and zygosity. The baseline cohort consisted of 1,260 respondent female pairs in this age group. To be included in the study, both co-twins had to agree to participate. Reasons for nonparticipation were refusal (106 pairs), poor health status (85 pairs), or death (6 pairs) of one or both twin sisters. The zygosity of the twin pairs was confirmed using a battery of 10 highly polymorphic gene markers in DNA extracted from a venous blood sample. Finally 103 monozygotic (MZ) and 114 dizygotic (DZ) twin pairs arrived at the laboratory where clinical examination and several tests of health and functional capacity were performed. On arrival, the participants provided a written informed consent. The study was approved by the ethics committee of the Central Finland Health Care District.

Bone assessments

Peripheral quantitative computed tomography (XCT 2000, Stratec Medizintechnik GmbH, Pforzheim, Germany) scans were obtained from the lower leg on the side of the dominant hand. The scanned sites were 55% (tibial shaft structural bending strength and muscle cross-sectional area) and 5% (distal tibia structural compressive strength) of the length of the tibia proximal to the distal end of the tibia. The analysis of the pQCT images was performed with software designed for analyzing cross-sectional CT images (Geanie 2.1, Commit; Ltd, Espoo, Finland). The cross-sectional area of the lower leg muscles (mCSA) was measured from the pQCT images by manually defining the boundaries between muscle
and bone as well as muscle and subcutaneous fat. To separate the bone from the surrounding soft
tissues density thresholds of 280 mg/cm$^3$ and 130 mg/cm$^3$ were used in the tibial shaft and in the distal
tibia, respectively. In the tibial shaft, bone marrow was excluded from the analysis with a density
threshold of 100 mg/cm$^3$. The total cross-sectional area (ToA) was determined for both tibial sites. The
main outcomes for bone were the section modulus of the tibial shaft (bone bending strength index,
BSIbend, in g) and the compressive strength of the distal tibia (BSIcomp, in g$^2$/cm$^4$). BSIbend was
determined as the density-weighted polar moment of inertia divided by the square-root of the total
cross-sectional area of the bone. BSIcomp was calculated as a product of volumetric bone mineral
density squared and total cross-sectional area, where the first term denotes the apparent compressive
strength of bone tissue (~ a material property) and the latter the load-bearing cross-sectional area.$^{30,31}$

Data on mCSA were obtained from 195 MZ and 218 DZ individuals, data on BSIbend from 197 MZ
and 220 DZ, and data on BSIcomp from 196 MZ and 216 DZ individuals. Two pairs (1 MZ pair, 1 DZ
pair) had missing data on all three variables. The main reasons for missing bone and muscle
measurements or analyses were: substantial movement artifacts during scanning, leg did not fit into the
gantry of the pQCT device, inaccurate positioning of the leg and metal in the tissues in the scanned
region.

Diseases, medication and physical activity

Self-reports of acute and chronic diseases, medication, smoking and physical activity had been obtained
earlier by a questionnaire and were confirmed by a physician during the clinical examination. Those
who reported using hormone replacement therapy (HRT) currently or had used it for at least one year
during the last 6 years were considered to be HRT users. Those who reported taking systemic
corticosteroid treatment currently or who had done so it for at least one year during the last six years
were classified as corticosteroid users.
Those reporting no other physical activity but light walking no more than twice a week at the most were rated as sedentary in the classification of current physical activity. Those reporting walking or other light exercise at least three times a week, or exercise of moderate intensity up to two times a week, were rated as moderately active. If a participant reported moderate or vigorous exercise at least three times per week, she was rated as active.\(^{(32)}\)

Data analysis

The equality of the means of the continuous variables and the equality of the distributions of the categorical variables between the groups of MZ and DZ individuals were analyzed with the Wald test and the equality of variances was tested with the variance ratio test, taking into account the dependence of observations between co-twins (Stata 8.0, Stata Corp.). The within-individual correlations for the whole sample and cross-twin cross-trait correlations separately for the MZ and DZ groups were calculated using Pearson’s correlation coefficient. The within-pair resemblance in each bone characteristic was estimated separately for the MZ and DZ groups using intra-class correlation coefficients (ICC) (SPSS 14.0, SPSS Inc.). ICCs can be used to obtain indicative estimates of the genetic and environmental components of the variances.\(^{(33)}\)

In quantitative genetic analyses, the variance of a trait can be decomposed into additive genetic effects (A), nonadditive genetic effects (D), shared environmental effects (C) and individual environmental effects (E). These analyses on twin data are based on the comparison of phenotypic resemblances within MZ and DZ co-twins. MZ co-twins share 100% of their genes, and DZ co-twins share, on average, 50% of their segregating genes. Thus, the higher phenotypic similarity between MZ co-twins than DZ co-twins points to the presence of genetic effects. A refers to the sum of the effects of the individual alleles over the loci, whereas D refers to interactions between alleles at the same or different loci.\(^{(33)}\) C includes factors that are shared by both co-twins, and these effects are expected to contribute
equally to the similarity within the MZ and DZ pairs. E are exposures that are not shared by the co-
twins, such as diseases and accidents that have affected only one sibling and thus, these factors
contribute to the observed differences within the twin pairs. The possible genetic models that can be
tested are the full models (ACE and ADE) and their submodels (AE, CE and E). The model with D but
not A (DE) is biologically implausible and hence not tested, while D and C cannot be estimated in the
same model (ADCE) using data that comprise twin pairs reared together.\(^{(34)}\)

Univariate genetic analyses were carried out to evaluate the genetic and environmental contributions to
each phenotype separately (mCSA, BSIbend, BSIcomp). A trivariate independent pathway model\(^{(34, 35)}\)
was used to investigate whether all the three traits mCSA, BSIbend and BSIcomp - share genetic
and/or environmental effects. This multivariate genetic analysis utilizes the cross-twin cross-trait
covariances within MZ and DZ pairs.\(^{(36)}\) The full trivariate independent pathway model consists of the
genetic and environmental effects that are common to all three traits \((A_c, C_c, E_c)\) and of the genetic \((A_1,
A_2, A_3)\), shared environmental \((C_1, C_2, C_3)\), and individual environmental \((E_1, E_2, E_3)\) effects that are
specific to each trait. The analysis was started with the hypothetical full ACE trivariate model. To
obtain a more parsimonious model, the full model was modified by dropping the non-significant or
smallest parameters one by one. In addition, genetic and environmental correlations were derived from
bivariate Cholesky decomposition models to evaluate the extent of common genetic and environmental
effects between each pair of variables.

The univariate and multivariate genetic analyses were performed with Mx software\(^{(37)}\) using the full
information maximum likelihood method with raw data input. In all the genetic analyses age was used
as a covariate. The alternative univariate and multivariate models obtained were compared against the
full model by Akaike’s information criterion \(\text{AIC} = -2 \times \log\text{-likelihood} - 2 \times \text{degrees of freedom}\),
which is smaller for better fitting models, and by the p-value of the \(\chi^2\) difference between the models.
The means and standard deviations are given for the characteristics of the MZ and DZ groups, and 95% confidence intervals are reported for the ICCs and the estimates of genetic analyses.
RESULTS

The MZ and DZ groups did not differ significantly in prevalence of cerebrovascular disease (Wald test, p=0.67), rheumatoid arthritis (p=0.18) or hip or knee osteoarthritis (p=0.23). Also, proportions of corticosteroid users (p=0.073), HRT users (p=1.0), smokers (0.42), persons with previous fractures (p=0.81), and persons in the different categories of physical activity (p=0.51) did not differ between the groups. However, variances of age and BSIcomp differed between the groups (Table 1). The within-individual Pearson’s correlation between mCSA and BSIbend was 0.45 (p<0.001), between mCSA and BSIcomp 0.31 (p<0.001) and between BSIcomp and BSIbend 0.53 (p<0.001).

The univariate models

Since the ICCs for bone traits were significantly higher but no more than 2-fold higher in MZ than DZ pairs, the ICCs suggested the presence of additive genetic and shared environmental effects (Table 2). Therefore, the univariate genetic analyses were based on the ACE model. The age-adjusted univariate models are presented in Table 3. The effect of age explained less than 1% of the variance in mCSA and BSIbend and 3% of the variance in tibial BSIcomp. The AE models showed good fit for mCSA, tibial shaft ToA, BSIbend, distal tibia ToA and BSIcomp whereas the CE and E models showed poor fit compared to the full ACE model (Table 3). In the AE models for these variables, the proportion of variance accounted for by genetic effects varied from 75% to 88%. Although the lower limit of 95% confidence interval for C was 0 in the ACE models of the bone strength variables, and thus the path was not statistically significant, the point estimates for the proportion of C of the variance were considerable (21% for BSIbend and 26% for BSIcomp). Therefore, the trivariate analysis was started with the full ACE model.
The multivariate models

The cross-twin cross-trait and within-individual Pearson's correlation coefficients for MZ and DZ twins are presented in Table 4 and suggest the presence of genetic effects on the associations between the traits. The final trivariate independent pathway model (-2LL=2436.8, df=1224, AIC=-11.2, p-value of the $\chi^2$ difference compared to the full model = 1.00) (Fig. 1) was obtained by dropping the smallest and non-significant parameters from the original full model (-2LL=2436.8, df=1219, AIC=-1.2). The paths that were eventually dropped were the following in the original full model: the path of common C to mCSA (estimate 0%, 95% CI: 0-7%), specific A to mCSA (0%, 0-51%), specific C to mCSA (1%, 0-24%), specific C to BSIbend (0%, 0-18%) and specific C to BSIcomp (0%, 0-26%). The final trivariate model showed that the total relative contributions of A, C and E were, respectively, 75%, 0% and 25% for mCSA, 55%, 20% and 25% for BSIbend and 40%, 37% and 23% for BSIcomp. The model also showed the presence of genetic factors common to all three variables. These factors accounted for 75% of the variance in mCSA, 17% of that in BSIbend and 8% of that in BSIcomp. Trait-specific genetic effects accounted for 38% of the variance in BSIbend and 32% of that in BSIcomp. In addition, 20% of the variance in BSIbend and 37% of that in BSIcomp was explained by shared environmental effects common to these bone traits. Individual environmental effects common to all three traits accounted for 5%, 22% and 13% of the variances of mCSA, BSIbend and BSIcomp, respectively. The rest of the variances in the variables were explained by trait-specific individual environmental effects. Dropping C completely from this model worsened the fit significantly (-2LL=2480.3, df=1226, AIC=28.3, p<0.001).

According to the bivariate Cholesky models the genetic correlations were as follows: between mCSA and BSIbend 0.46 (95% CI 0.33-0.57), between mCSA and BSIcomp 0.43 (0.23-0.66) and between BSIbend and BSIcomp 0.51 (0.20-0.72). The respective environmental correlations were 0.42 (0.25-0.57), 0.34 (0.15-0.50) and 0.68 (0.55-0.78).
DISCUSSION

The results of this study showed that the association between cross-sectional area of the lower leg muscles and tibial bone structural strength has its origin in both genetic and environmental factors. Muscle cross-sectional area is highly heritable while interindividual differences in tibial strength are moderately affected by genetic factors.

Our results on the degree of heritability of muscle cross-sectional area are supported by previous studies in which the heritability of lean mass measured with DXA has varied from 56% to 84%. Knowledge on the heritability of muscle cross-sectional area, however, is sparse. In a study by Prior et al. the heritability of the cross-sectional area of calf muscles was 23%. This estimate was obtained after including several covariates in the analysis and thus, the estimate is not comparable with ours. In addition, the heritability of the cross-sectional area of the upper limb muscles may differ from that of the lower leg muscles. The former has been reported to be over 90%, but the result was found in a rather small sample of twins. Muscle cross-sectional area has higher heritability than muscle strength or muscle power; genetic effects explain ~30% to 50% of the variance in these traits.

Genetic factors seem to have a notable influence on bone strength. Animal studies have found large differences in bone strength between mouse strains from different genetic lineages with the heritability being ~70%. In humans, however, the heritability of estimated bone strength seems to be lower. The heritability of the section modulus of the femoral neck measured by dual energy x-ray absorptiometry (DXA) has been reported to be 40-55%, which is similar to that of the section modulus (BSI_bend) of the tibial shaft in our analysis (55%). The heritability of bone strength in the lower limbs seems to be lower than that of aBMD or vBMD, which is shown to be 70% to 80%, or bone cross-sectional area as shown in our study. Also, our previous study suggested that the
heritability of structural bone strength is lower in the lower limb than in the upper limb, while the heritability of vBMD and area is similar in the lower and upper limb.\(^{(46)}\) Apparently, environmental factors have a more substantial effect on the structural bone strength of weight-bearing bones than non-weight-bearing bones. This is plausible as it is not bone mass per se but the strength of the whole bone that adapts to the demands of the environment. On the assumption of regular locomotive loading the contribution of environmental effects can be expected to be proportionally large to the bone strength of the lower limbs. This is supported by studies, which have found larger differences in bone strength indices than in bone mineral density between athletes and controls.\(^{(21, 48)}\)

Associations between muscle and bone have been observed in several studies.\(^{(13-17, 22)}\) Often, the same association has been interpreted merely as the influence of muscle force on bone traits. However, lean mass and aBMD seem also to have common genetic effects which contribute to the covariance observed between these traits\(^{(24, 25)}\) The results of our analyses on pQCT-derived muscle cross-sectional area and structural bone strength indices are line with the previous findings. It is likely that this genetic association between muscle and bone is caused by influence of several different genes. Previous studies suggest that the vitamin D receptor (VDR) gene may be one of the genes since the same polymorphism of the VDR gene (Fok I) has been found to be associated with bone mineral density\(^{(49)}\) and lean mass.\(^{(50)}\) In addition, polymorphisms of myostatin which is a known negative regulator of muscle mass\(^{(51)}\) have also been found to be associated with aBMD.\(^{(52)}\) Other possible mechanisms underlying the genetic association may be IGF-I and androgen receptors. IGF-I is an important growth factor in both muscle and bone tissue\(^{(53, 54)}\) and IGF-I gene promoter polymorphism is shown to be associated with bone geometry and strength indices, fractures\(^{(55)}\) and muscle phenotypes.\(^{(56)}\) Association of an androgen receptor gene polymorphism with fat-free mass\(^{(57)}\) and aBMD\(^{(58)}\) have also been found. However, it is good to notice that according to the trivariate model, the absolute amount of genetic effects shared by muscle and bone is small although the genetic correlation
between bone and muscle is relatively high. This is due to moderate heritability of bone strength. Further, the results show that the majority of the genetic influence on bone strength is independent of genetic regulation of muscle cross-sectional area.

According to the results, the bending strength of the tibial shaft and compressive strength of the distal tibia are largely affected by different genes although they also share some genetic effects. Our previous study\(^{46}\) showed that with respect to compressive strength the distal radius and distal tibia shared their genes totally. Both these epiphyseal bone sites have a similar bone structure composed of both trabecular and cortical bone and are evolutionarily designed for bearing compressive reaction forces during quadrupedal locomotion. In contrast, the tibial shaft is almost entirely cortical bone and provides a stiff lever arm for muscle activity to facilitate locomotion. In other words, different bone structures are the result of the different functions performed at different bone sites.\(^{59}\) Since the distal and diaphyseal bone sites have different functions, and their structure and proportions of cortical and trabecular bone are different, it is plausible that they are regulated, at least partly, by different genes.

Although genetic factors had a large influence to the cross-sectional area of the lower leg muscles and a moderate influence on bone strength, environmental factors had a considerable influence on both of these traits. Our analyses showed that muscle area and bone strength share some common environmental effects. Genetic analyses conducted without information on specific environmental factors cannot, of course, reveal what these environmental factors are; however, previous studies offer some implications as to their nature. Physical activity is likely to be one of these factors since both muscle mass and bone traits are known to improve in response to the same exercise program.\(^{60, 61}\) Similarly, periods of disuse of the lower limbs lead to impairment in both their muscle mass and bone structure.\(^{62-65}\) Further, nutrition\(^{66}\) and some medicines may add to common environmental effects. For example, glucocorticoid treatment\(^{67}\) and hormone replacement therapy\(^{68, 69}\) influence properties
of both muscle and bone. Besides being affected by the same individual environmental factors, the compressive and bending strength of tibia were also influenced by the same shared environmental factors. This may be due to environmental factors that influenced bone strength in childhood, when co-twins are likely to have grown up in a similar environment. The influences of exercise and nutrition on bone in childhood may partly be maintained to adulthood and, in women, even to postmenopausal years.\(^70\text{-}72\) A recent animal study\(^73\) has suggested that the intrauterine environment, i.e. maternal nutrition during pregnancy, may also have substantial effects on bone in adulthood. However, it must be recalled that these shared environmental effects analyzed in this study also include environmental factors that are similar in co-twins in adulthood.

An important strength of our study was that the measurements were performed with pQCT which provides precise information on bone structure\(^27\) and also enables the assessment of muscle cross-sectional area. Previous studies estimating the common genetic background of muscle and bone have used DXA to measure lean mass and aBMD,\(^24\text{-}26\) but due to its planar nature DXA-derived aBMD cannot adequately capture the most important aspects of bone structural strength.\(^19\) Further, analysis of the associations between lean mass and BMD measured with DXA may be problematic, since the accuracy of aBMD is compromised by soft tissue disparities within the measured bone sites\(^74\) Despite the fact that our sample was population-based, the inclusion criteria may have led to the exclusion of pairs with at least one sister in poor health. This may have reduced the variance of the bone phenotypes, increased the similarity within the pairs and thus influenced the heritability estimates. Since our sample consisted of older white women, the results probably cannot be generalized directly to other populations or age-groups since heritability estimates are age- and population-specific. However, the age group studied is especially interesting in view of the increased risk of these women for osteoporosis, bone fragility and sarcopenia.
In conclusion, this study provides new information on the regulation of muscle and bone tissue. Since muscle mass and bone strength were partly influenced by the same genetic and environmental factors in older women, it is clear that some genetic and environmental factors may predispose to or, conversely, protect from both sarcopenia and bone fragility.

ACKNOWLEDGEMENTS

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**TABLE 1 CHARACTERISTICS OF GROUPS OF TWIN INDIVIDUALS**

<table>
<thead>
<tr>
<th></th>
<th>Monozygotic individuals</th>
<th>Dizygotic individuals</th>
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<th>p†</th>
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<tr>
<td>Age (yrs)</td>
<td>199 68.3 (3.7)</td>
<td>222 68.9 (3.1)</td>
<td>0.21</td>
<td>0.02</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>199 157.8 (6.2)</td>
<td>222 159.1 (5.8)</td>
<td>0.10</td>
<td>0.33</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>199 69.2 (11.3)</td>
<td>222 70.0 (11.3)</td>
<td>0.59</td>
<td>0.94</td>
</tr>
<tr>
<td>mCSA (cm²)</td>
<td>195 63.7 (9.5)</td>
<td>218 63.6 (10.3)</td>
<td>0.97</td>
<td>0.26</td>
</tr>
<tr>
<td>BSIbend (g)</td>
<td>197 1.59 (0.25)</td>
<td>220 1.59 (0.26)</td>
<td>0.96</td>
<td>0.46</td>
</tr>
<tr>
<td>BSIcomp (g²/cm^4)</td>
<td>196 0.66 (0.19)</td>
<td>216 0.65 (0.23)</td>
<td>0.59</td>
<td>0.03</td>
</tr>
</tbody>
</table>

mCSA, muscle cross-sectional area; BSIbend, bone bending strength index; BSIcomp, bone compressive strength index

*Adjusted Wald test
†Variance ratio test
**TABLE 2** WITHIN-PAIR INTRA-CLASS CORRELATION COEFFICIENTS (ICC)

<table>
<thead>
<tr>
<th></th>
<th>MZ</th>
<th></th>
<th>DZ</th>
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<td></td>
<td>ICC</td>
<td>95% CI</td>
<td>ICC</td>
<td>95% CI</td>
</tr>
<tr>
<td>mCSA</td>
<td>0.73</td>
<td>(0.62-0.81)</td>
<td>0.42</td>
<td>(0.25-0.57)</td>
</tr>
<tr>
<td>BSIbend</td>
<td>0.73</td>
<td>(0.62-0.81)</td>
<td>0.50</td>
<td>(0.35-0.63)</td>
</tr>
<tr>
<td>BSIcomp</td>
<td>0.73</td>
<td>(0.62-0.81)</td>
<td>0.56</td>
<td>(0.41-0.68)</td>
</tr>
</tbody>
</table>

mCSA, muscle cross-sectional area; BSIbend, bone bending strength; BSIcomp, bone compressive strength
### Table 3: Univariate Genetic Models Adjusted for Age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model fit</th>
<th>Standardized estimates (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model</td>
<td>-2LL</td>
</tr>
<tr>
<td>mCSA</td>
<td>ACE</td>
<td>1070.7</td>
</tr>
<tr>
<td></td>
<td>AE</td>
<td>1070.7</td>
</tr>
<tr>
<td></td>
<td>CE</td>
<td>1090.1</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>1161.6</td>
</tr>
<tr>
<td>Tibial shaft</td>
<td>ToA</td>
<td>298.4</td>
</tr>
<tr>
<td></td>
<td>AE</td>
<td>299.1</td>
</tr>
<tr>
<td></td>
<td>CE</td>
<td>319.1</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>411.5</td>
</tr>
<tr>
<td></td>
<td>BSIbend</td>
<td>1854.5</td>
</tr>
<tr>
<td></td>
<td>AE</td>
<td>1856.4</td>
</tr>
<tr>
<td></td>
<td>CE</td>
<td>1867.3</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>1955.9</td>
</tr>
<tr>
<td>Distal tibia</td>
<td>ToA*</td>
<td>1170.4</td>
</tr>
<tr>
<td></td>
<td>AE</td>
<td>1170.5</td>
</tr>
<tr>
<td></td>
<td>CE</td>
<td>1224.6</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>1337.5</td>
</tr>
<tr>
<td></td>
<td>BSIcomp*</td>
<td>1666.9</td>
</tr>
<tr>
<td></td>
<td>AE</td>
<td>1670.3</td>
</tr>
<tr>
<td></td>
<td>CE</td>
<td>1679.1</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>1774.4</td>
</tr>
</tbody>
</table>

A, additive genetic effects; C, shared genetic effects; E, individual environmental effects
mCSA, muscle cross-sectional area; ToA, total cross-sectional area; BSIbend, tibial shaft bending strength; BSIcomp, distal tibia compressive strength

-2LL, -2 times log-likelihood; df, degrees of freedom; ΔAIC, difference in the Akaike’s information criterion between the model and full model; p, p-value of the $\chi^2$ difference between the model and full model

* Published earlier (46)
**TABLE 4** INTRA-PAIR CROSS-TWIN AND WITHIN INDIVIDUAL PEARSON’S CORRELATION COEFFICIENTS FOR MONOZYGOTIC (MZ) AND DIZYGOTIC (DZ) TWINS.

<table>
<thead>
<tr>
<th></th>
<th>mCSA twin 1</th>
<th>BSIbend twin 1</th>
<th>BSIcomp twin 1</th>
<th>mCSA twin 2</th>
<th>BSIbend twin 2</th>
<th>BSIcomp twin 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MZ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mCSA twin 1</td>
<td>0.46</td>
<td>0.34</td>
<td>0.74</td>
<td>0.24</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>BSIbend twin 1</td>
<td>0.54</td>
<td>0.40</td>
<td>0.36</td>
<td>0.73</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>BSIcomp twin 1</td>
<td>0.35</td>
<td>0.56</td>
<td>0.15</td>
<td>0.17</td>
<td>0.73</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>DZ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mCSA twin 2</td>
<td>0.42</td>
<td>0.14</td>
<td>0.05</td>
<td>0.35</td>
<td>0.21</td>
<td>0.45</td>
</tr>
<tr>
<td>BSIbend twin 2</td>
<td>0.32</td>
<td>0.51</td>
<td>0.45</td>
<td>0.43</td>
<td>0.45</td>
<td>0.45</td>
</tr>
<tr>
<td>BSIcomp twin 2</td>
<td>0.20</td>
<td>0.26</td>
<td>0.58</td>
<td>0.33</td>
<td>0.66</td>
<td></td>
</tr>
</tbody>
</table>

mCSA, muscle cross-sectional area; BSIbend, tibial shaft bending strength; BSIcomp, distal tibia compressive strength

The correlations of the MZ pairs are above the diagonal and the correlations of the DZ pairs below the diagonal.
FIG. 1. REDUCED ACE INDEPENDENT PATHWAY MODEL FOR CROSS-SECTIONAL AREA OF THE LOWER LEG MUSCLES (mCSA), STRUCTURAL BENDING STRENGTH OF TIBIAL SHAFT (BSIBEND) AND STRUCTURAL COMPRESSIVE STRENGTH OF DISTAL TIBIA (BSICOMP). THE PERCENTAGES (95% CONFIDENCE INTERVALS) ARE THE PROPORTIONS OF THE TOTAL VARIANCE OF EACH VARIABLE EXPLAINED BY EACH GENETIC AND ENVIRONMENTAL FACTOR.