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Original Article

Influence of Heredity and Environment on Bone Density in Adolescent Boys: A Parent–Offspring Study

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Abstract. The purpose of the present parent–offspring study was to investigate the influence of heredity and environment on bone density in young men. Another aim was to discover whether the same genetic factors influence bone mass, lean mass and muscle strength. Fifty families including a father, mother and one son were investigated. The mothers (aged 44.5 ± 4.4 years) and fathers (aged 47.1 ± 4.4 years) generally had a sedentary lifestyle with little physical activity. As a contrast, all but three of the sons (aged 17.0 ± 0.4 years) were active in ice hockey training. Bone mineral density (BMD, g/cm^2) of the total body, head, lumbar spine and femoral neck was measured using dual-energy X-ray absorptiometry. Muscle strength of the hamstrings and quadriceps muscles was also measured in the boys. BMD values of different sites in the fathers, mothers and sons were adjusted for weight, height, age, and any significant influence of environment. Heritability estimates were obtained as regression coefficients with the boys' adjusted BMD as dependent variable and the adjusted midparent bone density (father BMD + mother BMD/2) as independent variable. Accordingly, heritability explained 34–54% of the variation in the sons' BMD. Midparent BMD of several sites also predicted the boys' lean mass and quadriceps strength, and midparent–offspring differences in lean mass predicted midparent–offspring differences in BMD of the total body, head and spine (β = 0.30–0.51, p<0.05). The sons were found to have almost 30% higher femoral neck BMD than their fathers, and physical activity (hours/week) predicted BMD at several sites among the sons β = 0.26–0.34, p <0.05). In conclusion, heritability is a main determinant of the variance in BMD in young men. Based on the results we suggest that the same genetic factors may influence bone mass, lean mass and muscle strength by affecting body size. The present study also emphasizes the importance of physical activity for the development and maintenance of BMD in men.

Keywords: Bone density; Heredity; Men; Muscle strength; Physical activity

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Introduction

The incidence of osteoporosis has increased in both sexes since the 1950s in most Western societies, but perhaps especially in men [1,2]. The bone mineral density (BMD, g/cm^2) has been demonstrated to be the best predictor of the future risk of fracture [3] and it has been demonstrated that peak bone mass probably accounts for at least 50% of the variation in bone mass even in the very elderly [4]. Therefore, to establish the predictors of BMD just after the rapid increase in BMD during the pubertal growth spurt period would probably increase the possibilities for effective preventive strategies.

The main determinant of BMD in adults is probably heritability [5–7], although the evidence is somewhat inconsistent. More than 20 years ago, Smith and colleagues [8] demonstrated that BMD of the forearm was more similar in monozygotic than in dizygotic twins, suggesting that the variation in BMD is determined at least in part by genetic factors. This work was later extended by several groups, showing that about 80% of the variation in bone density might be determined by genetic factors. However, because of

violation of some of the assumptions associated with analysis of twin data, the estimates are too high in some studies [7]. Parent–offspring studies, measuring the degree of resemblance between parents and their children, can also be used to estimate the degree of influence of heritability on the variation in BMD. Accordingly, Krall and Dawson-Hughes [9] demonstrated in a study including 40 families that heritability explained about 50% of the variation in BMD after adjustments for significant environmental factors.

Weight and physical activity are other factors highly associated with BMD [10,11]. Body weight, acting through gravity, is constantly affecting the weight-bearing part of the skeleton, explaining, at least in part, the strong association with bone density demonstrated in both children [10] and adults [12]. We recently demonstrated that the type of weight-bearing physical activity undertaken is an important determinant of BMD in adolescent boys [11]. Muscle strength has also been demonstrated to be a strong predictor of BMD [13]. A strong muscle might increase BMD by creating high strains in adjacent bones. However, muscle strength has been demonstrated to be a significant predictor also of BMD of distant bones [11], indicating a more general relationship as well.

The purpose of the present parent–offspring study was to investigate the influence of heredity on bone density in adolescent boys in relation to environmental factors such as physical activity and body constitution. Another aim was determine whether the same genetic factors might influence the variation in bone mass, muscle strength and lean body mass in the same group.

Material and Methods

Subjects

Sixty-four families including a father, mother and one son were asked to participate in this study. Of these families, six did not want to, or could not participate for various reasons, and eight families were excluded because of medications or diseases known to affect bone density, leaving 50 families in the study. The boys, aged 17.0 ± 0.4 years (range 16.4–18.1 years), had previously all been active in ice hockey training to varying degrees, and all but three were still active in intensive ice hockey training. At the time of testing the average weekly training time was 8.9 ± 2.8 h (range 4–18 h). The three remaining boys had stopped playing ice hockey about 1 year before this investigation but were instead active in soccer and bandy ball training, respectively. All boys were also participating in 2 h of general physical education training in school every week. None of the boys smoked.

Using a standardized questionnaire and interviews, information was collected regarding the mothers' and fathers' work during the previous 5 years, and their physical activity level (hours/week) during the previous 5 years. Smoking habits were recorded as present smoker (1) or non-smoker (0). Physical activity (hours/week) was defined as physical exercise combined with sweating or breathlessness. The mothers were also investigated concerning use of the contraceptive pill and irregularity of menses, defined as no menses for at least 3 consecutive months.

The mothers were 44.5 ± 4.4 years (range 33.7–52.2 years) old. Four of the mothers (8%) were postmenopausal. These four subjects did not have significantly lower BMD at any site than the rest of the mothers. The contraceptive pill was currently being used by five of the mothers (10%) and 10 (20%) were smokers. The average amount of physical activity was 2.1 ± 2.6 h/week (range 0–15 h). Twenty-six (52%) of the mothers stated that they had trained at most 1 h/week during the last 5 years. Thirteen (26%) classified their work as sedentary. The fathers were aged 47.1 ± 4.4 years (range 39.0–57.2 years) and nine (18%) were smokers. The average amount of training every week was 2.2 ± 2.6 h (range 0–15 h). Twenty-one (42%) of the fathers stated that they had trained at most 1 hour/week during the last 5 years and 24 (48%) classified their work as sedentary.

The parents and their sons gave their written informed consent to participate in this study. The study was approved by the Ethics Committee of the Medical Faculty, Umeå University.

Methods

Fat mass, lean body mass and areal BMD of the head were derived from a total-body scan and the autoanalysis program, using a Lunar DPX-L (Lunar, Madison WI) dual-energy X-ray absorptiometer, software version 1.3y. The head was defined as the whole head including the first four cervical vertebrae. To maximize the precision the centering option was used and scaling was set to about 200. The right femoral neck BMD was obtained using the femur software, and the lumbar spine (L2–4) BMD, bone mineral content (BMC, grams), bone area (cm^2), and height were obtained using the spine software. Since areal BMD (g/cm^2) is affected by the bone size, volumetric bone mineral density (vBMD, mg/cm^3) was also estimated for the lumbar spine [14]. It was then assumed that this site is cylindrical in shape. The volume of this cylinder can be estimated from the area and height. The vBMD is then estimated as (BMC/volume) × 1000 (mg/cm^3). In our laboratory, the coefficient of variation (CV value; SD/mean) for a total body scan is 0.7% [15] and the CV values for the femur software and spine software are 1.5% and 1%, respectively. Using the same procedure, the CV values were estimated to be 0.9% and 2.6% for lean body mass and fat mass, respectively [15]. To minimize the interobserver variation, all analyses were made by the same investigator.

Isokinetic Muscle Strength

Isokinetic muscle strength of the right quadriceps femoris and hamstrings muscles in the boys was measured in newton-meters (N m) using a Biodex isokinetic dynamometer (Biodex, New York, NY). The subject was seated with a 120° hip angle with the lever attached just above the ankle. The dynamometer's axis of rotation was aligned with the knee joint and the angular movement of the knee joint was 90°. Each subject made five maximal consecutive repetitions at 90° per second and 10 at 225° per second. The rest between change of velocities was approximately 30 s. The highest peak torque for each velocity was used in the correlation analysis. Three of the 50 boys could not participate due to injuries at the time of the testing.

Clinical Measurements

Height and body weight were measured in stockinged feet and underwear using standardized equipment. Body mass index (BMI) was calculated as weight (kg)/ height $(m)^2$.

Statistics

An analysis of variance (ANOVA) was used to test differences between the fathers, mothers and sons. The BMD values for the fathers, mothers and sons were adjusted for the influence of age, weight and height, according to linear regression equations and means for each group and bone site. Each bone site was also adjusted for any significant influence of physical activity and the parents' BMD was also adjusted for any significant influence of smoking habits. Differences between the smoking and non-smoking parents were investigated using a nonparametric test for independent samples (Mann–Whitney). Adjusted midparent bone density [(BMD mother + BMD father)/2] (Z_P) and adjusted offspring bone density *Z*-scores (Z_O) were then computed separately based on the standard deviations and means in each group and for each bone site:

$$Z_P = \text{bone density}_P - \text{mean}_P/\text{standard deviation}_P$$
$$Z_O = \text{bone density}_O - \text{mean}_O/\text{standard deviation}_O$$

In a population, the phenotypic variance can be divided into genetic variance and nongenetic variance. Genetic variance is further broken down into additive, which is transmissible between generations, and nonadditive, which includes interactions among multiple loci and dominance variance. The nongenetic variance consists of common environmental factors and it should be realized that this factor is often present in a large amount and is often difficult to overcome by experimental design [16].

The heritability (h_2) is defined as the ratio of additive genetic variance (V_a) to phenotypic variance (V_p) [16]:

$$h_2 = V_a/V_p$$

Heritability estimates that include only additive genetic variance (e.g. midparent–offspring comparisons) are termed 'heritability in the narrow sense' (h_N^2). In the present study, heritability in the narrow sense was estimated from the regression coefficient (b_p) of the adjusted midparent bone density *Z*-scores (*z*bone density_P) in linear regression models where the adjusted offspring's bone density *Z*-score (*z*bone density_O) was the dependent variable, that is:

$$z\text{bone density}_O = \text{constant} + b_p(z\text{bone density}_P)$$

In the present study it was assumed that the children's bone density could be explained from the multiple regression model:

$$\text{Bone density}_0 = h_2 + phys + ms + bc + height + e$$

Where h_2 is heritability, that is the adjusted midparent bone density of each site; phys is physical activity (hours/week); *ms* is lean body mass and muscle strength of the quadriceps and hamstrings muscles; *bc* is body constitution, i.e. weight, height, BMI and fat mass; and *e* is on error term, that is the environmental factors not investigated in the present study and measurement errors. Since many of the explanatory variables were found to be highly intercorrelated ($r > 0.8$, $p<0.001$), a principal component analysis (PCA) was conducted to avoid the consequences of multicollinearity, i.e., imprecise regression parameter estimates. The principal components (PCs) formed from the original variables were then used in a multiple regression model to evaluate in the boys the independent relationship between bone density at different sites and the explanatory variables above. PCA is a statistical technique that linearly transforms an original set of variables into a substantially smaller set of uncorrelated variables. PCA searches for a few linear combinations of the original variables that capture most of the information (variance) of the original variables [17]. Geometrically, the first PC is the line of closest fit to *n* observations in the multidimensional variable space. The second PC is the line of closest fit to the residuals from the first PC, and so on. The PCs are sometimes rotated if the unrotated PCs are difficult to interpret. Probably the most frequently used orthogonal rotation is Varimax, and this rotation was also used in the present study. In short, the Varimax rotation results in new perpendicular coordinate axes where the original variables have either small or large rotated component loadings, resulting in PCs that are easier to interpret. The rotated component loadings are the original variables' correlation with the PC that they form. The SPSS statistical package (SPSS, Chicago, IL) for PC was used for the statistical analysis. A *p* value less than 0.05 was considered significant.

Results

Physical characteristics and results of BMD measurements are presented in Table 1.

Table 1. Anthropometric data, and different BMD measurements, among the boys, mothers and fathers, respectively

	Boys	Mothers	Fathers
Age (years)	17.0±0.4	44.5±4.4	47.1±4.4[b,c]
Weight (kg)	72.5±8.6	65.6±10.3	83.9±13.3[a,b,c]
Height (cm)	178±6.8	164±5.4	178±4.6[a,c]
BMI (kg/m^2)	22.8±2.5	24.3±3.3	26.6±4.1[a,b]
Lean body mass (kg)	57.3±5.1	39.4±3.5	58.4±5.9[a,c]
Fat mass (kg)	11.9±5.3	23.3±8.0	21.9±8.6[b,c]
Physical activity (h/week)	8.9±2.8	2.1±2.6	2.2±2.6[b,c]
BMD (g/cm^2)			
Total body	1.23±0.07	1.16±0.07	1.21±0.08[a,c]
Head	1.99±0.16	2.36±0.20	2.13±0.17[a,b,c]
Lumbar spine	1.27±0.12	1.23±0.14	1.15±0.13[a,b]
Femoral neck	1.24±0.12	0.95±0.11	0.96±0.11[b,c]
Volumetric BMD (mg/cm^3)			
Lumbar spine	356±30	381±41	324±37[a,b,c]

Values are the mean ± SD.
BMI, body mass index.
[a] Significant difference when comparing father and mother, $p<0.05$.
[b] Significant difference when comparing father and son, $p<0.05$.
[c] Significant difference when comparing mother and son, $p<0.05$.

Heritability estimates were calculated by adjusting the fathers', mothers' and sons' BMD for weight, height, age, and any significant influence of physical activity and smoking habits at each bone site according to linear regression equations. Thus, all bone sites among the fathers were also adjusted for amount of physical activity, the mothers' BMD values of the total body and head were adjusted for smoking habits, and the sons' BMD values of the total body, femoral neck and lumbar spine were adjusted for the influence of physical activity (hours/week). After converting midparent BMD and the sons' BMD to *Z*-scores, heritability explained 34% of the variation in the sons' total-body BMD (confidence interval (CI) = 0.08–0.60, $p<0.05$), 54% (CI = 0.30–0.79) of head BMD, 43% (CI = 0.16–0.67) of femoral neck BMD, 38% (CI = 0.11–0.65) of lumbar spine BMD ($p<0.01$) and 50% (CI = 0.24-0.76) of vBMD of the spine. Heritability estimates were also calculated without the four families where the mothers were postmenopausal. Accordingly, heritability explained 31% (total-body BMD), 52% (head BMD), 56% (femoral neck BMD), 32% (spine BMD) and 44% (spine vBMD) of the variation.

The independent predictors of the boys' BMD of different sites and spine vBMD were evaluated by means of a multivariate analysis. The explanatory variables, that is the boys' weight, height, BMI, fat mass, lean body mass, quadriceps strength and hamstrings strength at 90° and 225° per second, and physical activity, were first transformed into four PCs. The first PC consisted of weight, BMI and fat mass, and the second PC consisted of hamstring strength, lean body mass and height (Table 2). The third and fourth PCs consisted of quadriceps strength and physical activity, respectively. These four PCs and the adjusted midparent BMD of each site were then used in a multiple regression analysis to explain the boys' BMD of each site (Table 2). The adjusted midparent BMD was an independent predictor of all BMD sites investigated, and spine vBMD, and the best predictor of BMD at all sites, except the boys' total-body BMD. Physical activity was an independent predictor of BMD of the total body, femoral neck and spine, but not of the head (Table 2).

Using linear regression, midparent BMD of the total body predicted the boys' lean body mass and quadriceps strength significantly, at both velocities measured (Table 3). Midparent BMD of the spine was significantly correlated with the boys' lean body mass, and midparent spine BMD and midparent femoral neck BMD predicted

Table 2. The independent relationship between the boys' total body BMD, head BMD, femoral neck BMD, spine BMD and spine volumetric BMD, and body weight, fat mass and BMI (principal component 1), lean body mass, height and hamstrings strength (principal component 2), quadriceps strength (principal component 3), physical activity (principal component 4) and adjusted midparent bone density of each site

Dominant content of each principal component	Bone site				
	Total body	Head	Spine		Femoral neck
			BMD	vBMD	
1. Body weight Fat mass BMI	0.37[a]	0.33[b]	0.09	−0.08	−0.04
2. Lean body mass Height Hamstrings strength	0.02	0.02	0.25[b]	−0.07	−0.12
3. Quadriceps strength	0.26[b]	0.29[b]	0.13	−0.04	0.31[b]
4. Physical activity	0.34[a]	0.11	0.26[b]	0.14	0.32[a]
Midparent bone density of each site	0.33[a]	0.45[a]	0.45[a]	0.56[a]	0.38[a]
R^2	0.48[a]	0.39[a]	0.38[a]	0.31[a]	0.44[a]

Midparent bone density was adjusted for age, height, weight, and any significant influence of physical activity and smoking habits. Beta values, *p* values and R^2 values are presented.
vBmD, volumetric BMD; BMI, body mass index.
[a] $p<0.01$; [b] $p<0.05$.

Table 3. The relationship between midparent bone density and the sons' lean body mass, and muscle strength of the thigh

Parameters of the boys	Midparent bone density				
	Total body	Head	Spine		Femoral neck
			BMD	vBMD	
Lean body mass	0.30[b]	0.21	0.33[b]	0.21	0.26
Quadriceps strength 90°/s	0.47[a]	0.21	0.30[b]	0.13	0.31[b]
Quadriceps strength 225°/s	0.38[a]	0.12	0.27	0.11	0.24
Hamstrings strength 90°/s	0.26	0.21	0.19	0.15	0.26
Hamstrings strength 225°/s	0.15	0.11	0.05	0.11	0.07

Beta values and *p* values are presented.
vBMD, volumetric BMD.
[a] $p<0.01$; [b] $p<0.05$.

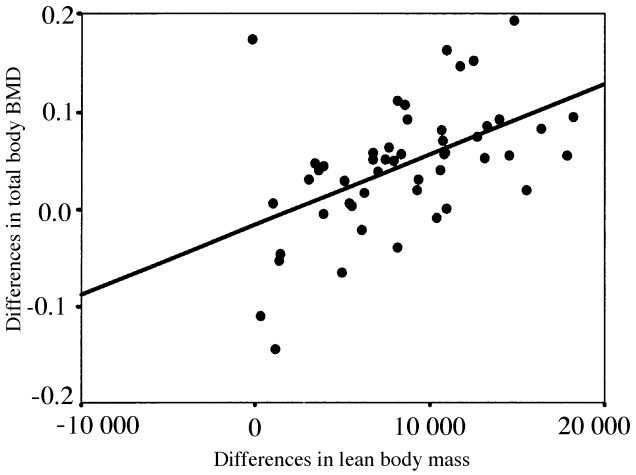

Fig. 1. Midparent–offspring difference in lean body mass (grams) plotted against midparent–offspring difference in total-body BMD (g/cm^2). Beta = 0.51, $p<0.001$, $R^2 = 0.2593$.

the boys' quadriceps strength at 90° per second (Table 3).

The midparent–offspring differences in lean body mass were found to significantly predict the midparent–offspring differences in total-body BMD ($\beta = 0.51$, $p<0.001$), spine BMD ($\beta = 0.39$, $p = 0.005$) and head BMD ($\beta = 0.43$, $p = 0.002$), but not femoral neck BMD ($\beta = 0.28$, $p = 0.05$) and spine vBMD ($\beta = 0.00$, $p>0.05$). The midparent–offspring differences in lean body mass are plotted against the differences in total-body BMD in Fig. 1.

Discussion

The first aim of the present study was to investigate the influence of heredity on BMD in adolescent boys, in relation to different environmental factors such as physical activity. Since areal BMD is affected by bone size volumetric BMD was also estimated for the lumbar spine [14]. In the present study, heritability according to its narrow-sense definition explained 34–54% of the variation in the sons' BMD at the different sites investigated. It seems that the heredity estimates were generally lower compared with those found in previous twin studies. This may have several explanations. Heritability is by definition the genetic variance divided by the total variance. The total variance, in the denominator, is the variance attributed to genetic factors plus the nongenetic variance. The nongenetic variance represents environmental factors, and in the present study the parents and offspring had significantly different lifestyles, at least concerning physical activity. This could have increased the environmental variance, and then subsequently decreased the estimated variation in bone density attributed to heritability by its definition. Some of the difference most probably also reflects different study designs. Most previous studies evaluating the influence of heredity on bone density have used the twin model, and about 80% of the variation in BMD has been attributed to heritability [5–7]. However, many studies have found heritability estimates of more than 100%, or unreasonable high estimates [6,7]. Accordingly, Slemenda and colleagues [7] evaluated the impact of genetic factors in 171 twin pairs and critically considered the results. The results showed lower intraclass correlations between the monozygotic twins than heritability estimates. This must reasonably indicate a violation of some assumption associated with analyzing twin data, since the genes of monozygotic twins are identical and must therefore be considered as an upper limit for heritability. In parent–offspring studies, on the other hand, the heritability estimates will be affected by the difference in age between the parents and their children. In the present study, the boys were about 17 years old with little variation. Since adolescence is a time of rapid bone accumulation, differences in development would increase the nongenetic variance among the boys. This might have influenced the estimated proportion of variance attributed to heritability. We also investigated the possibility that the four postmenopausal women would decrease the estimates of heredity due to a more rapid bone loss during and after menopause. However, excluding these

women increased the heritability estimate only of the femoral neck.

With these facts in mind, parent–offspring studies generally result in lower estimates of the influence of heredity on bone density. Jouanny et al. [18] investigated the importance of genetic factors in 129 nuclear families and found that BMD of the total body in the children was significantly associated with that of their parents ($r = 0.30$, $p < 0.0001$). Krall and Dawson-Hughes [9] investigated 160 members of 40 adult families and found heritability to explain 46–62% of the variation in BMD at different sites. It seems that the present study supports previous studies and suggests that heritability is an important factor determining the variation in bone density during late puberty in boys. The fact that physical activity was also an independent significant predictor of the sons' BMD in the present study implies that environmental factors are important for the development of peak bone density in men.

In the present study all but three of the sons were active in intensive junior ice hockey training, while many of the fathers were overweight and about half stated that they had a sedentary job with little or no physical activity. Interestingly, the sons were found to have an almost 30% higher femoral neck BMD compared with their fathers, although the fathers had a much greater body weight. A subgroup of boys from the present study has also been compared with a group of adult ice hockey players with a mean age of 25 years [19]. The adult ice hockey players were found to have 10% higher BMD of the femoral neck than the subgroup from the present study, indicating that the boys in the present study have not yet reached their peak bone mass, which would increase the difference compared with the fathers' BMD. Furthermore, 28 boys involved in ice hockey training from the present study were compared with 24 age-matched boys with a low level of physical activity [11]. The ice hockey group was found to have about 9% higher BMD of the femoral neck. With these facts in mind, it seems that the difference in femoral neck BMD between the fathers and sons in the present study is a result of a highly physically active lifestyle in the sons and a sedentary lifestyle in the fathers. Admittedly, early middle age in men might be related to bone loss by age per se, even though we have not found such a report. BMD of the fathers in the present study was also compared with the BMD of males in a study from the southern part of Sweden [20]. Those authors presented the data as normative, and interestingly the men (aged 40–49 years) investigated in that study showed equivalent BMD of the total body, femoral neck and spine as in the present study.

Another aim of the present study was to determine whether the same genetic factors might influence the variation in bone mass, muscle strength and lean body mass. Previous studies concerning the relationship between BMD and muscle strength are not conclusive. Site-specific relationships have been demonstrated between muscle strength and BMD of the adjacent bones [13,21]. This might indicate a potential for muscle-strengthening exercises to increase BMD [22]. However, the present study and others [13,15,21] have demonstrated relationships between muscle strength and BMD also of distant bones, indicating a more general relationship between BMD and muscle strength. In the present study we also found midparent BMD to predict the boys' lean body mass and quadriceps muscle strength, and the midparent–offspring difference in lean body mass predicted the midparent–offspring difference in bone density. Furthermore, spine BMD was adjusted for the influence of bone size by estimating volumetric bone density. Interestingly, in the boys muscle strength did not predict spine volumetric BMD independently, and midparent spine volumetric BMD did not predict the boys' muscle strength and lean body mass. These results indicate a general association between bone mass, lean body mass and muscle strength, hypothetically mediated by some genes influencing these parameters by affecting size during late puberty in boys. This suggestion is supported by a recent study in which Seeman and associates [23] investigated the associations between muscle strength, lean body mass and bone density in 56 monozygotic and 56 dizygotic twins. The authors concluded that more than half the covariance in BMD of the femoral neck and lean body mass was attributed to the same genetic factors. It was also suggested that the association between muscle strength and BMD might be determined by genes regulating body size.

In conclusion, the present parent–offspring study has demonstrated heritability according to its definition to be an important determinant of the variation in bone density during late puberty in boys. However, the results also suggest that physical activity is important for achieving the highest possible peak bone density, and that a sedentary lifestyle might be associated with substantial bone loss in men. Based on the results we also suggest that the same genetic factors influence the variation in bone mass, lean body mass and muscle strength in adolescent boys by influencing body size.

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