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Hip Geometry, Bone Mineral Distribution, and Bone Strength in European Men and Women: The EPOS Study

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Hip geometry and bone mineral density (BMD) have been shown previously to relate, independently of each other, to risk of hip fracture. We used Lunar DPX "β" versions of hip strength analysis (HSA) and hip axis length (HAL) software to analyze scans from ten representative age-stratified population samples in the European Prospective Osteoporosis Study (EPOS). All 1617 subjects were >50 years of age, and 1033 were women. The data were modeled with gender and center as categorical variables. The bone mineral density of the upper half of the femoral neck declined at a faster rate with age than that in the lower half. Femoral neck cross-sectional moment of inertia (CSMI), a measure of resistance to bending, showed no significant age reduction in either gender. However, height and weight effects on CSMI were significantly more beneficial in men than in women ($0.002 < p < 0.012$) and the weight effect appeared to be mediated by bone mineral content (BMC). Compressive stress (Cstress), defined as the stress in the femoral neck at its weakest cross section arising from a standardized fall, was higher in women. Although Cstress increased with body weight when BMC was held constant, in practice it fell through the association and statistical interaction of rising body weight with rising BMC. HAL, as expected, was strongly positively associated with male gender and also height ($p < 0.0001$). Hip strength-related indices were markedly center-dependent. Significant differences ($p < 0.0001$) were noted between the centers for all the variables investigated that related to hip geometry. Adjustment for femoral neck bone mineral content (totBMC) showed these center differences to account for >50% of center variation in hip strength, which remained highly significant ($p < 0.0001$). We conclude that there are substantial geographical differences in femoral neck geometry as well as in BMD. These geometric variations may contribute to the large variations in hip fracture risk across Europe. The effects of aging on hip strength need to be explored in longitudinal studies. (Bone 27:151–159; 2000)

Key Words: Osteoporosis; Hip fracture; Bone mineral density; Hip strength; Epidemiology; Biomechanics.

Introduction

Age-specific hip fracture rates[14] are highly variable in Europe, more so than vertebral deformity prevalence rates.[26] The reasons for this are poorly understood. A bone fractures when subjected to stresses greater than its ultimate strength. At any timepoint, the stress within a bone depends on its geometrical structure, the mechanical properties of the material of which the bone is made, and the direction and size of the force applied.[1,7,10,13,20] The major force applied to the hip during locomotion is that of bending. As the ground reaction force is applied, a tensile stress results on the superior surface, whereas, on the inferior surface, the force creates a compressive stress. A fall on the greater trochanter reverses the direction of these forces.[21] When the combination of tensile and compressive stresses exceeds the ultimate yield strength of the hip, it fractures.

Early attempts to estimate the effects of variable hip geometry

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were made by Phillips et al.[29] using radiographic images. Martin and Burr[24] extracted the information contained within dual-energy photon absorptiometry (DPA) scans and quantified the amount and distribution of bone within a two-dimensional projection of the three-dimensional structure. The technique was developed further by Beck et al.[3] and applied to data from updated dual-energy X-ray absorptiomety (DXA). Interest in the geometric distribution of bone mineral has increased with the demonstration that secular changes have occurred in the UK[27] and New Zealand,[30] which might explain in part the marked secular increases in risk of hip fracture seen in those two countries in the last three decades. Previous studies have used hip strength analysis to estimate the risk of hip fracture,[36] and Beck et al.[2] studied changes in femoral geometry with age in a large population-based survey of American subjects. There were geometric differences seen between selected samples of American and Japanese women.[25] These and other data suggest that complex genetic and environmental influences affect femoral neck geometry.[32]

The purpose of this study is to present the descriptive epidemiology of indices relevant to hip strength in European men and women >50 years of age, examined in an age-stratified, multicenter, population-based prevalence study of vertebral deformity. We applied computer programs developed[15,33] and validated by others to analyze hip strength (hip strength analysis, HSA)[36] and to measure hip axis length (HAL)[15] in a large cross-sectional (prevalence) study, the European Vertebral Osteoporosis Study (EVOS). EVOS was the precursor to the European Prospective Osteoporosis Study, an incidence study of fracture and its determinants, which was based in 35 centers in 19 European countries. During the recruitment phase, or shortly after, many subjects submitted to bone densitometry of the proximal femur by DXA. In ten centers, Lunar DPX or DPX-L densitometers were used. This allowed us to measure HSA and HAL in a large number of subjects. We investigated, using statistical modeling, the effects of age and anthropometric variables, gender and geographic location, on hip axis length and hip strength.

Materials and Methods

Populations

Nine of the centers from different countries that took part in the study (see Table 2) were participants in the EVOS, which has now entered its prospective phase as the European Prospective Osteoporosis Study (EPOS). EVOS was a prevalence study in which each center aimed to recruit 600 subjects, aged 50–80 years, as an age-stratified random sample of their local population using local population registers. The tenth center, Cambridge, recruited subjects aged >65 years using similar principles. Cambridge originally recruited >2000 subjects, who were measured several years earlier on Hologic equipment. For the present study, Cambridge subjects from two of the ten participating primary care practices were recruited as a randomized subsample[23] and were rescanned using a Lunar DPX-L device. In the first nine centers, proportions of sample populations selected for and agreeing to bone densitometry varied by center.[22,23] We previously sought but found no evidence of bias[22,23] arising from incomplete recruitment to densitometry, the principle cause of which was limited resources.

Cross-calibration of Densitometers

Each of the densitometers was cross-calibrated using the European spine phantom (ESP). The ESP is a semianthropomorphic phantom with three "vertebrae" of known densities, 0.5, 1.0, and 1.5 g/cm^2.[18] At least five measurements were made on each machine and a linear regression was fitted through the points. Unlike our previous experience with the ESP prototype, good fits to the data were possible using linear regression. The intercept of each line was forced through zero. The mean regression coefficients for each machine were compared and used for cross calibration so that all machines could be scaled against each other. This procedure was followed for both bone mineral density (BMD, in grams per square centimeter) and bone mineral content (BMC, in grams). Because all machines were made by the same manufacturer and of the same type, the effects on the results obtained were to make small linear adjustments between densitometers to remove the slight differences observed between the results obtained on similar machines when phantoms are scanned.[28]

For the HSA parameters, cross-sectional moment of inertia (CSMI), cross-sectional area (CSA), compressive stress (Cstress), and tensile stress (Tstress), the cross-calibration coefficients for BMC were applied as a multiplicative function of the conversion factor used when calculating the path length of the X-ray through bone.

Pencil-beam machines do not generate images that are intrinsically magnified, unlike fan-beam or cone-beam X-ray devices. We assumed that lengths measured by these Lunar machines would be highly accurate and precise, because all calculated length measurements depend on distances traversed by the scanner beam, which in turn depend directly for their identity, on the close control of manufacturing tolerances practiced by the manufacturer. Therefore, we made no attempt to cross calibrate for distance measurements.

Bone Densitometry and Hip Strength Analysis

All subjects underwent standard bone density measurement of the proximal femur, using Lunar DPX scanners according to the manufacturer's protocol, except that, for larger subjects, the scanned area's width was increased if necessary to allow inclusion of the whole acetabular region. The image data files were analyzed locally, then reanalyzed centrally, by one operator, using the "β" version of HSA, along with standard bone density and HAL measurements. All software was provided by Lunar Instruments Corp. (Madison, WI).

The HSA program permits calculation of bone geometry and bone distribution within the femoral neck from a planar scan performed by a Lunar DPX bone densitometer. X-ray absorption data are extracted from the output image data file and the amount of bone and its distribution are calculated. The device then provides geometric measurements to enable single plane engineering analysis of the individual proximal femur within the zone defined by the usual 1.5-cm-wide femoral neck region of interest. The operator first places four regions of interest on the DXA image. The first is the center of the femoral head, at the center of an expandable circular region, which is matched as closely as possible to the outline of the femoral head. Next, the femoral neck region of interest is reviewed for accurate placement, and the femoral neck axis placed as accurately as possible along its center. Finally, the femoral shaft axis is defined centrally along the shaft. The computer program then iteratively assesses all cross sections in the femoral neck region of interest and identifies the plane with the least resistance to bending, which is used in all subsequent calculations.

The program then calculates and displays a list of all the calculated geometric and densitometric values. The CSMI is the measure of a bone's resistance to bending in the weakest plane. For a given amount of bone within the femoral neck, the further the bone is distributed from the center of mass within the cross

section, the more rigid it is. The CSMI is calculated by integrating, with respect to distance from the plane of neutral loading (defined by two-dimensional beam theory), the projected bone thickness profile across the bone axis.[3] Yoshikawa et al.[36] validated these measurements by studies on cadaver specimens and noted good correlations between DXA-calculated values and direct measurements of cadaver ($r^2 = 0.96$) and aluminum step-wedge-phantom ($r^2 = 0.99$) CSMI values. The predicted force applied to the greater trochanter during a "standard" fall is then derived from observational relationships between fall force, height, and weight.[31] Fall force is resolved geometrically to give a compressive force parallel to the neck axis and a bending force perpendicular to the neck axis. The perpendicular force produces a mechanical bending moment dependent on the magnitude of the resultant force and the distance from the center of the femoral head to the weakest point of the femoral neck that colocates with minimum CSMI. The compressive force and bending moment are then combined, using the standard Euler beam theory to calculate the total compressive stress (Cstress) at the weakest point.[36] The fall index (FI) is calculated as the ratio of the yield stress of the superior femoral neck in compression to Cstress. If Cstress is greater than yield stress (FI < 1) a fracture is predicted. Yield stress of cortical bone is derived from the data of Burstein.[6]

The safety factor (SF) is calculated using the same principles, using the force generated during walking. This force is calculated as 2.5 times body weight at an angle of 13° from vertical.[34] Once again, the forces are resolved in the two perpendicular directions, this time resulting in a compressive force down the femoral neck and a tensile bending force on the superior cortex. The result of these two is a tensile stress (Tstress) on the superior cortex. By dividing this into the value for tensile yield stress,[6] SF is calculated as an indication of the resistance to fracture of the femoral neck while walking.

Precision

Analysis precision was investigated using 20 randomly selected scans and both inter- and intraoperator variability examined. The 20 scans were analyzed by three different operators to assess the interoperator precision. The analysis was then repeated in a blind manner, by a single operator, after intervals of 1 and 6 months, to assess intraoperator precision. Results are expressed as coefficients of variation (%CV).

Statistics

The following variables (with their units of measurements in parentheses) were investigated as outcome variables or else as intermediary variables with the potential to explain mechanical and biological aspects of fracture risk: CSMI (mm^4), neck BMD (totBMD, g cm^{-2}), neck BMC (totBMC, g), upper and lower BMD (upBMD and lowBMD, g cm^{-2}) of the standard femoral neck region split at the midline, neck diameter (mm), compressive stress (Cstress, MPa), tensile stress (Tstress, MPa), FI (dimensionless), SF (dimensionless), and HAL (mm). For Cstress and Tstress it should be noted that 1 MPa = 1 N mm^{-2}. The data were modeled using multiple analyses of variance with gender and center as categorical variables and age, height, and weight as covariates in the model, using the SPSS statistical analysis package (SPSS Inc., Chicago, IL) and JMP version 3.1 (SAS Institute Inc., Cary, NC). Potential interactions between covariates were investigated and removed systematically from the various models if found not to be statistically significant at the 95% confidence level ($p < 0.05$). The effects of aging and other continuous variables were investigated using multiple regression analysis. Covariance analysis was used to investigate the dependence of variables of interest on combinations of continuous and categorical variables. To allow meaningful comparisons between centers when the mean age, weight, and height of the subjects differed, in some analyses the data were first adjusted to values of these parameters close to the mean for the whole population (age 65 years, weight 70 kg, height 165 cm). Because their residuals were consistently lognormally distributed in various models Cstress, Tstress, and SF were modeled after log-transformation. The other variables of interest showed normally distributed residuals and did not require transformation.

Table 1. Analysis of precision

Parameter (units)	Intraoperator (%CV)	Interoperator (%CV)
CSMI (mm^4)	3.8	4.1
CSA (mm^2)	2.1	2.6
Upper FN BMD (g cm^{-2})	2.6	2.2
Lower FN BMD (g cm^{-2})	1.1	1.3
Cstress (MPa or N/mm^2)	6.9	12.9
Tstress (MPa)	9.9	15.9
HAL (mm)	0.7	1.3
Neck diameter (mm)	1.5	1.6
Total FN BMD (g cm^{-2})	1.6	1.5
Safety factor (dimensionless)	11.6	17.5
Fall index (dimensionless)	7.4	12.7

KEY: BMD, bone mineral density; CSA, cross-sectional area; CSMI, cross-sectional moment of inertia; Cstress, compressive stress; CV, coefficient of variation; FN, femoral neck; HAL, hip axis length; Tstress, tensile stress.

Modeling Strategy

There are many outcome variables of potential interest generated by hip strength analysis. In line with our overall objective, we modeled descriptively all outcomes we thought to be of possible interest, particularly with reference to age, gender, geographical center, and anthropometry. In any cross-sectional study involving subjects in their eighth decade or older, healthy survivor effects as well as cohort effects will make the statistical effects of age at best qualitatively indicative of the effects of aging in the individual, at worst unrepresentative. In our further modeling we focused on effects that were independent of age, which appeared to influence the load-related outcome variable of primary interest to us, Cstress, a measure of the mechanical compressive stress (MPa) induced in the superior femoral neck at its weakest point by a standardized fall.[36] We chose Cstress as our index of interest rather than FI because FI is already calculated as an age-dependent function (since Burstein found yield stress to be age-dependent[6]).

Results

Precision

Intraoperator variability was better than the interoperator variability (**Table 1**). The parameters with the highest level of precision were the distance measurements, neck diameter and HAL (1.52% and 0.66%). The composite parameters that depended on combinations of bone distribution and distance measurements were the least precise.

Scans Submitted

Analysis was done on 1875 scans. Some were excluded prior to analysis on the basis of the presence of air (n = 176) or because

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Table 2. Numbers of subjects with analyzable scans from each center

Center	Men	Women	Both
1. Cambridge	48	61	109
2. Kuopio	63	105	168
3. Leuven	92	134	226
4. Szczecin	38	80	118
5. Warsaw	53	113	166
6. Zagreb	29	43	72
7. Rotterdam	174	217	391
8. Oslo	77	126	203
9. Athens	10	59	69
10. Prague	—	95	95
Total	584	1033	1617

the region scanned was too small or poorly positioned, resulting in insufficient pelvic separation (n = 64). Postanalysis, those scans that had parameter values that were >3 standard deviations from the mean were reexamined for poor positioning or the presence of osteoarthritis. On this basis, a further 18 scans were rejected. Thus, the rejection rate for scans submitted was 13.8%.

Descriptive Characteristics of the Population Studied

Of the total of 1617 subjects used for this study (**Table 2**), the smallest sample size came from Athens (n = 69) and the largest from Rotterdam (n = 391). The ratio of men to women was 1:1.77, and this was similar for all centers (1:1.3–1:2.1), except Athens (1:5.9) and Prague, which scanned their male subjects on another manufacturer's machine. **Table 3** provides further details of the subjects studied.

Effects of Center

Table 4 shows the mean values of totBMD, HAL, and Cstress, adjusted to age 65 years, for men and women according to center. These data were then modeled by adjusting them for height and weight and their significant interactions with center and gender.

Even after adjusting for age, gender, height, and weight there were still significant between-center differences in HAL, Cstress (Table 4), as well as in Tstress, SF, FI, and CSMI in both men and women. To investigate the dependence of these between-center differences in bone mineral content the parameters were further adjusted for totBMC. For all parameters the between-center differences remained significant ($p < 0.0001$). For CSMI, SF, and FI the addition of totBMC into the model reduced the variance that could be explained by the observed center differences (CSMI: 1.46% to 0.33%; FI: 5.6% to 4.9%; SF: 5.6 to 5.1%), whereas for the other three parameters the percentage of variance attributable to center increased (HAL: 3.20% to 3.42%; Cstress: 4.55% to 5.35%; Tstress 4.95% to 5.01%). Only for CSMI was there a substantial part of the between-center differences explained by between-center differences in totBMC (**Table 5**).

Theoretical Risk of Fracture

The theoretical threshold for a hip fracture after a typical fall on the greater trochanter occurs at FI = 1.0. Therefore, the proportion of subjects with FI < 1.0 were calculated. It can be seen from **Figure 1** that, after adjusting to age 70 years and body weight 70 kg, the differences in proportions of subjects between the ten centers with FI < 1.0 were highly significant for women, but not for men (for women $\chi^2 = 39.6$, $p = 0.00001$; for men $\chi^2 = 14.3$, $p = 0.075$). The reason for this gender difference in p values was attributed to the small number of men with FI < 1.0.

Effects of Gender and Anthropometric Measurements on Hip-strength-related Variables After Adjustment for Center and Bone Mineral Content

To analyze further the differences between genders with regard to outcome variables, the interactions of gender with age, height, and weight were analyzed (**Table 6**). For all these outcome variables, men and women were significantly different, with men having higher values, with the exception of Cstress and Tstress, which were lower (indicating greater strength in men). This resulted in significantly higher mean values in men for FI (1.75 vs. 1.36, $p < 0.0001$) and SF (6.42 vs. 4.99, $p < 0.00001$) after adjusting to age 65 years, weight 70 kg, and height 165 cm. The effect of body weight on CSMI after adjusting for the same variables was significantly different between genders being greater in men (an increase of 7.08%/10 kg in women and 8.23%/10 kg in men; $p < 0.001$ for both). However, adjusting in addition for totBMC removed the significance of the effect of weight in both genders, suggesting that weight affects CSMI through its effect on totBMC. Increasing totBMC was more advantageous for CSMI in men than in women (men: 24% increase per gram increase in totBMC, women: 18% increase per gram increase in totBMC; $p < 0.001$). The effect of height on

Table 3. Descriptive statistics of age, height, and weight by center

	Women			Men		
Center	Age (ys)	Height (cm)	Weight (kg)	Age (ys)	Height (cm)	Weight (kg)
1	74.5 (2.5)	158.8 (7.3)	64.2 (11.9)	75.1 (2.4)	170.8 (6.3)	74.2 (9.7)
2	72.2 (4.6)	157.9 (5.9)	67.6 (10.5)	67.8 (5.1)	171.1 (4.8)	79.3 (8.2)
3	62.1 (7.6)	158.6 (5.8)	68.8 (10.4)	62.9 (8.6)	170.4 (6.2)	78.7 (9.9)
4	65.0 (5.8)	159.3 (5.4)	70.0 (13.3)	66.6 (7.1)	171.5 (5.2)	82.2 (12.5)
5	65.2 (7.8)	155.3 (6.0)	67.9 (11.3)	70.1 (7.7)	168.3 (6.9)	79.9 (12.0)
6	64.3 (8.1)	162.4 (6.2)	73.7 (12.5)	62.0 (7.4)	172.6 (7.4)	83.2 (10.9)
7	67.2 (7.9)	161.4 (6.5)	70.4 (11.5)	67.7 (7.8)	173.7 (6.7)	81.3 (10.3)
8	66.9 (8.1)	162.0 (7.1)	68.7 (11.9)	65.6 (8.6)	176.4 (7.1)	82.4 (12.1)
9	64.4 (6.6)	155.7 (5.3)	65.5 (9.5)	71.2 (7.1)	169.3 (8.5)	75.8 (10.5)
10	62.1 (6.2)	163.7 (6.4)	69.6 (12.2)			
Mean	66.3 (7.8)	159.7 (6.7)	68.8 (11.6)	67.2 (8.1)	172.2 (6.8)	80.2 (10.8)

Data expressed as mean (standard deviation).

Table 4. Total femoral neck bone mineral density, hip axis length, and compressive stress

	Data adjusted to age 65 only		Data adjusted for age, height, weight, and any significant interactions	
	Women	Men	Women	Men
(a) Total femoral neck BMD (g cm^{-2})				
Cambridge	0.803	0.950	0.825	0.919
Kuopio	0.832	0.956	0.843	0.910
Leuven	0.806	0.914	0.821	0.879
Szczecin	0.799	0.905	0.806	0.846
Warsaw	0.814	0.966	0.834	0.911
Zagreb	0.794	0.966	0.783	0.911
Rotterdam	0.825	0.921	0.826	0.868
Oslo	0.771	0.898	0.778	0.846
Athens	0.766	0.894	0.766	0.859
Prague	0.736	—	0.772	—
Mean	0.795	0.930	0.805	0.883
%CV	3.68	3.18	3.52	3.37
Center difference	$p < 0.0001$		$p < 0.0001$	
(b) Hip axis length				
Cambridge	105.7	121.5	107.8	117.1
Kuopio	104.0	118.2	108.4	114.3
Leuven	101.3	115.3	106.8	112.6
Szczecin	102.4	110.4	105.1	106.1
Warsaw	103.1	119.6	105.4	116.9
Zagreb	107.5	118.7	108.1	114.8
Rotterdam	104.6	118.9	108.8	114.5
Oslo	102.7	115.9	107.0	109.7
Athens	98.3	112.8	104.5	110.2
Prague	107.5		103.4	
Mean	103.7	116.8	106.5	112.9
%CV	2.73	3.03	1.73	3.22
Center difference	$p = 0.002$		$p < 0.0001$	
(c) Compressive stress (Cstress, MPa)				
Cambridge	129.9	108.2	131.5	103.6
Kuopio	116.2	106.2	121.4	95.7
Leuven	134.0	116.0	138.3	109.0
Szczecin	118.8	103.3	117.8	92.8
Warsaw	131.0	105.8	128.3	101.1
Zagreb	142.6	115.3	143.4	113.0
Rotterdam	142.3	124.9	137.2	108.1
Oslo	136.0	116.5	137.2	108.1
Athens	136.6	106.7	136.9	107.9
Prague	137.0		139.0	
Mean	132.4	111.4	132.8	104.1
%CV	6.71	6.36	6.13	6.29
Center difference	$p = 0.0001$		$p < 0.0001$	

Adjustments to age = 65 years; weight = 70 kg; height = 165 cm. Means are geometric means.

CSMI was somewhat less beneficial in men (women: increase of 14.56%/10 cm, men: increase of 14.17%/10 cm; $p = 0.037$ for the interaction of gender with the height effect), although this difference became nonsignificant after adjusting for totBMC. Height was associated inversely with totBMD in men (women: increase of 0.80%/10 cm height increment, men: decrease of 2.15%/10 cm; $p = 0.011$ for the interaction of gender with the height effect).

Effect of Age

In both genders, after adjusting for height and weight, there was an age-dependent decrease in upper and lower BMD (upBMD: −7.49%/decade in women, −5.32%/decade in men [for difference $p = 0.37$]; lowBMD: −3.83%/decade in women, −1.49%/decade in men [for difference $p = 0.009$]). TotBMD adjusted similarly decreased with age in both men and women, although the decrease was greater in women (women: 5.53%/per decade, men: 3.37%/decade; [for difference $p = 0.062$]).

CSMI in women, adjusted for height and weight, showed no significant change per decade of age ($p = 0.89$), whereas in men it showed an increase of 2.94%/decade ($p = 0.0094$; for difference $P = 0.031$) (**Figure 2**). When totBMC was included in the model relating CSMI to age, together with its interaction with gender, the effects of weight and the gender interactions with both weight and age all became nonsignificant. However, the positive effect of age on CSMI increased to 5.1% of the mean-adjusted female CSMI per decade of age. Neck diameter adjusted for height and weight also increased with age (Figure 2) in both genders. Although the rate of increase was higher in men, the rates of change per decade were not statistically different between genders (women: +1.26%/decade, men: +1.95%/decade; for difference $p = 0.087$). As a consequence of these various effects of age, FI fell significantly with age in women only (−0.07 units per decade, $p < 0.0001$), which mirrored a rise in Cstress with age (0.7% per decade; $p = 0.006$). Likewise, an age effect on SF was significant only in women (−3.8% per decade; $p < 0.0001$), reflecting the adverse effect of age on Tstress (+1.3% per decade; $p < 0.0001$).

Relationship Between Cstress, Weight, and BMC

Cstress was made the outcome variable of interest in a model that included center, gender, age, and weight. There were no significant interactions between center or gender and other independent variables of interest, and height was not a significant determinant. Due to the resulting increase in fall force on the proximal femur upon impact, Cstress tended to increase with increasing weight. However, heavier subjects tend to have higher totBMC. Cstress tended to decrease with increasing totBMC, because as totBMC increases, there is more bone available to dissipate the fall force. When totBMC was added to the model, age was no longer a significant determinant of Cstress, but the model was improved by including totBMC as a polynomial rather than a linear term (by adding the squares and cubes of totBMC), together with height, which now had a statistically significant effect that differed between genders. Weight alone accounted for 21.5% of the variance in this model and totBMC alone (with its square and cube) accounted for 1.6% of the variation, but together they accounted for 45.4% of the variation in Cstress, a substantial increase over the arithmetic sum of the individual effects of weight and totBMC. This increase in the explained variation occurred because the calculations were for type 3 sums of squares, which attribute effect sizes to determinants without allowance for the contributions of their interactions (in this case the interactions between totBMC and weight). Thus, the effect size of body weight on Cstress was an increase of 1.4 MPa per kilogram increase in body weight in the model with totBMC; however, after exclusion of totBMC from the model, this effect size decreased to a 0.9 MPa increase per kilogram increase in body weight. Because BMC tends to increase with body weight, in practice, heavier subjects often had lower Cstress values than lighter subjects, because the adverse effect of high body weight on Cstress was more than counterbalanced by the higher BMC values.

Discussion

The purpose of this study was to present the descriptive epidemiology of the results of hip strength analysis, as applied to

Table 5. Percentage of variance in the data explained by selected models for seven outcome variables of interest

Independent variates in model	totBMD	CSMI	HAL	Cstress	Tstress	FI	SF
Model 1: Center, gender, and age	27.2 (2.02)	55.8 (1.04)	55.0 (3.97)	13.9 (5.86)	19.2 (5.47)	16.1 (7.02)	20.8 (5.87)
Model 2: Center, gender, age, height, and weight	38.0 (2.37)	68.7 (1.10)	66.9 (3.32)	23.2 (4.55)	23.1 (4.95)	22.7 (6.62)	24.5 (5.60)
Model 3: Center, gender, age, height, weight, and totBMC	85.7 (0.85)	85.1 (0.30)	67.0 (3.42)	53.5 (5.35)	30.1 (5.00)	53.1 (5.10)	31.7 (5.09)

Values in parentheses indicate percent explained by differences between centers. The significance of the effect of center in all models for each of the seven outcome variables after adjusting for the effects of the other independent variables was $p < 0.0001$.
KEY: CSMI, cross-sectional moment of inertia; Cstress, compressive stress; FI, fall index; HAL, hip axis length; SF, safety factor; totBMD, total bone mineral density; Tstress, tensile stress.

Lunar DPX femur scans, in ten widely separated European centers. This was undertaken in the context of a population-based, age-stratified prevalence study of vertebral deformity and, although not all subjects in this prevalence study had bone density measurements due to resource constraints, we previously found no evidence of selection bias arising from this selection of subjects.[23] In earlier analyses we showed that there were marked variations over a threefold range between the prevalence of vertebral deformity in both men and women[26] and also substantial variations in bone density between centers.[22] In this study, we found substantial effects of age, gender, anthropomorphic measurements, and geographical center on indices related to hip strength.

This work had to be confined to the ten centers with Lunar DPX equipment because the software is machine-specific. Because the study used a single manufacturer's brand of machine, and the machines were cross calibrated with the European spine phantom, it is not believed that differences between centers in the results obtained would have been influenced to any substantial extent by residual differences in machine performance after cross calibration.[28] When the data were analyzed in relation to age, substantial age effects were discerned both in relation to bone density changes and changes in geometric indices. The two most striking age effects were a tendency for femoral neck width to increase in men and women and a tendency for femoral neck bone density to decrease in women, especially when considered in relation to values at younger ages in the superior femoral neck. In the case of men, the latter effect was considerably smaller, consistent with previous cross-sectional and longitudinal data from population-based samples in this age group (50–80 years).[8,11]

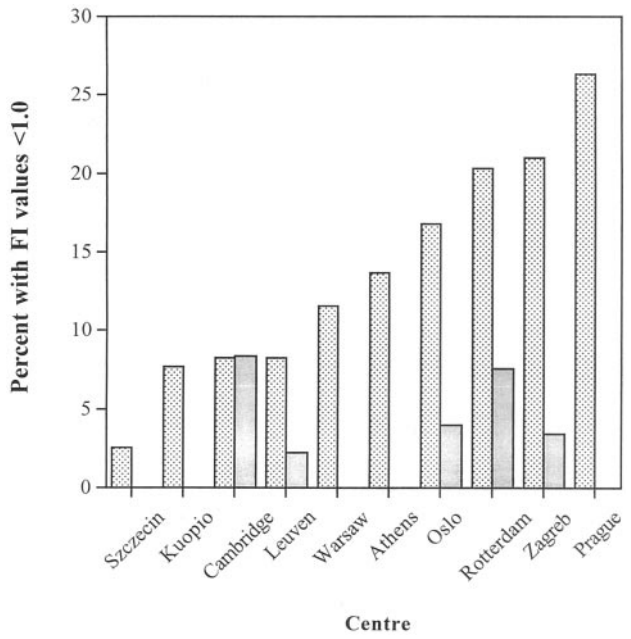

Figure 1. Proportions of male and female subjects with a fall index (FI) under the theoretical fracture threshold of 1.0, according to center. FI data were adjusted to age 70 years (but otherwise unadjusted) to remove effects of age differences between the different cohorts. Dotted bars: <1.0%, women; gray bars: <1.0%, men.

The interpretation of age effects in prevalence studies must be tempered with considerable caution because of the possibility that there may have been differences between age cohorts. In the present study it is conceivable, for example, that the privation and substandard nutrition experienced by some of our subjects during the Second World War might, at critical periods of their bone growth, have had a substantial influence on their femoral neck geometry or on their femoral neck bone density some 50 years later. Nevertheless, Garn[16] showed that, at other bony sites with a true periosteum, there is progressive enlargement of the periosteal envelope with age resulting from slow apposition of new bone. The femoral neck, in contrast to other tubular bones, is unusual in that it lies within the capsule of the hip joint. Havelka and Horn[17] showed that the alkaline phosphatase-positive cell layer associated with the periosteum and the osteoblasts immediately beneath it extends to join the so-called "tidemark" zone at the interface between bone and cartilage in ball joints such as the hip. Because of its strong association with bone formation, alkaline phosphatase expression in bone-associated cells suggests osteoblastic activity[4,5] and provides indirect evidence that the femoral neck is indeed capable of expanding its "periosteal" envelope in the same manner as other tubular long bones. If this were not the case, endosteal resorption of the femoral neck cortex would be uniquely dangerous at this site.

Whether or not it arises in association with aging, this difference in femoral neck width between our younger and older subjects provides considerable protection against the weakening effects of bone loss arising from remodeling imbalance in later life. For a given amount of bone within its cross section, a tubular structure such as the femoral neck increases in strength as its diameter increases, provided the stress-strain relationship remains linear.[2]

An important finding was that there were substantial differ-

Table 6. Differences between genders in seven outcome variables[a]

Outcome variable	Mean (95% CI) adjusted for age, height, center, and weight			Interactions with gender		
				Age	Height	Weight
	Women	Men	*p* (for adjusted difference)	*p* for interaction (positive values indicate a more positive effect in men)		
totBMD	0.807 (0.800–0.814)	0.885 (0.876–0.894)	<0.0001	0.021	−0.011	0.049
CSMI	11,743 (11,532–11,954)	16,534 (16,261–16,807)	<0.0001	0.030	0.012	0.002
HAL	106.8 (106.5–107.1)	114.6 (114.3–114.9)	<0.0001	n.s.[b]	n.s.	n.s.
Cstress	133.5 (131.6–135.4)	105.5 (103.6–107.5)	<0.0001	n.s.	n.s.	n.s.
Tstress	22.93 (22.4–23.4)	17.93 (17.46–18.41)	<0.0001	−0.006	n.s.	n.s.
FI	1.36 (1.34–1.38)	1.75 (1.72–1.78)	<0.0001	n.s.	n.s.	n.s.
SF	4.99 (4.89–5.09)	6.42 (6.26–6.59)	<0.0001	0.011	n.s.	n.s.

[a]See Table 5 for abbreviations.
[b]Not significant.

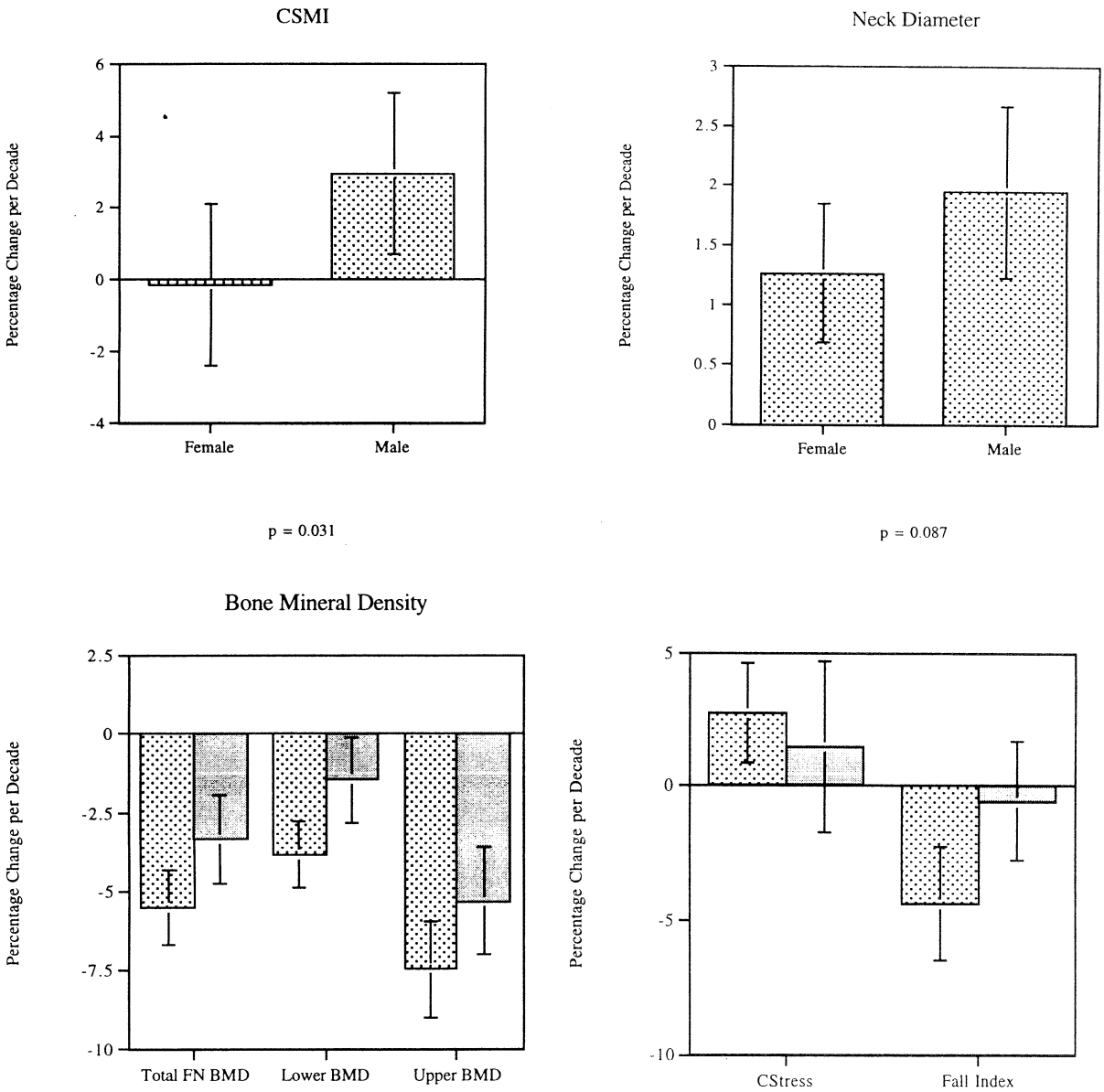

Figure 2. The effects of age on indices of interest in the two genders. *p* values test the null hypothesis that there is no difference between men and women in rate of change with age. Dotted bars: women; gray bars: men.

ences between centers in calculated hip strength that could not be accounted for by previously published differences between centers in mean bone density.[22] Differences in the geometric distribution of bone were at least as important in the determination of the between-center variation in hip strength as the differences in mean bone density, which themselves were shown previously to be sufficient to account for up to a 2.5-fold variation in hip fracture risk between centers.[22] A prevalence survey such as the present one cannot answer questions as to the biological origins of these geometric differences. In principle, they might arise from genetic differences between populations; differences in dietary, lifestyle, and anthropometric determinants integrated over the lifespan of the individual; or the possible interactions of these environmental factors with genetic risk determinants. Hip strength analysis generates indices that are directly related to the theoretical levels of mechanical loading that occur during a standardized fall. Therefore, ideally, data such as these should be carried forward into prospective studies to evaluate the predictive power of hip strength analysis for the identification of future hip fractures, with and without adjustment for bone density variation. Duboeuf et al.[12] already showed that upBMD is a better predictor than lowBMD of intracapsular hip fracture in elderly women. Our data strengthen considerably the case for developing new approaches to measuring fracture risk that go beyond the simple assessment of total hip BMD.

The gender differences in the determinants of hip strength indices were intriguing. The larger effect of body weight in men on cross-sectional moment of inertia (CSMI) and indices that depended on CSMI was itself dependent in part on the greater apparent rate of increase in neck diameter in men than in women, even though this difference in rate of increase in diameter was not highly statistically significant. However, CSMI is not dependent on neck diameter but rather on the square of neck diameter. The larger effect of weight on CSMI in men presents the possibility that mechanical loading had a bigger influence on the development of hip strength in men than in women, perhaps through its intermediary effect on totBMC. Others[19] have suggested that the beneficial effect of mechanical loading on bone strength in women is partly blunted by the absence of premenopausal levels of estrogen due to menopause. Estradiol levels, when they fall below measurable levels, account for an impressive fraction of total hip fracture risk in elderly women.[9] At least some of the effects of body weight on CSMI in women might therefore be attributable to the higher levels of endogenous estrogen in the heavier women rather than directly due to increased mechanical loading.

In conclusion, calculated hip strength in men and women varies substantially between different European populations due to both geometry and differences in hip BMD. Variation in hip strength is therefore a candidate mechanism to explain in part the very substantial[14] variations in hip fracture rate between different countries in Europe that are seen in both genders. Indices of hip strength decline with age in women but not men. This is because femoral neck width appears to increase with age and this compensates, at least in part, for the declining BMD. Body weight and femoral neck BMC together account for about 50% of the population variance in Cstress, a key theoretical determinant of fracture risk. Although high body weight considered in isolation tends to increase Cstress, because it increases load generated by a fall, this is more than compensated by the associated increases in BMC and cross-sectional moment of inertia of the femoral neck. This analysis did not consider the effects of increased soft tissue around the greater trochanter in softening the impact of a fall. Also, the present study did not assess a sufficient number of incident fractures to test the hypothesis that calculated hip strength explains the observed geographic variation in risk; indeed, it might be difficult to address this possibility in a prospective framework for reasons of resource constraints, although it could be addressed in a case-control study of DXA-measured hip strength performed in convalescence after hip fracture. Our data relating body weight and body mass index to hip strength offer a partial explanation as to why men and women with heavier body build are less susceptible to hip fracture. Future studies should investigate the lifestyle and dietary determinants of hip strength and also investigate the role of hip strength analysis as a predictor of fracture outcome.

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