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Original Article

Population-Based Geographic Variations in DXA Bone Density in Europe: The EVOS Study

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Abstract. The purpose of this study was to investigate variations in bone density between 16 European populations, 13 of which were participants in the European Vertebral Osteoporosis Study (EVOS). Men and women aged 50–80 years were recruited randomly from local population registers, stratified in 5-year age bands. The other three centres recruited similarly. Random samples of 20–100% of EVOS subjects were invited for dual-energy X-ray absorptiometry (DXA) densitometry of the lumbar spine and/or proximal femur using Hologic, Lunar or Norland pencil beam machines or, in one centre, a Sopha fan-beam machine. Cross-calibration of the different machines was undertaken using the European Spine Phantom prototype (ESPp). Highly significant differences in mean bone density were demonstrated between centres, giving rise to between-centre SDs in bone density that were about a quarter of a population SD. These differences persisted when centres using Hologic machines and centres using Lunar machines were considered separately. The centres were ranked differently according to whether male or female subjects were being considered and according to site of measurement (L2–4, femoral neck or femoral trochanter). As expected, bone mineral density (BMD) had a curvilinear relationship with age, and apparent rates of decrease slowed as age advanced past 50 years in both sexes. In the spine, not only did male BMD usually appear to increase with age, but there was a highly significant difference between centres in the age effect in both sexes, suggesting a variability in the impact of osteoarthritis between centres. Weight was consistently positively associated with BMD, but the effects of height and armspan were less consistent. Logarithmic transformation was needed to normalize the regressions of BMD on the independent variates, and after transformation, all sites except the femoral neck in females showed significant increases in SD with age. Interestingly, the effect of increasing weight was to decrease dispersion in proximal femur measurements in both sexes, further accentuating the tendency in women for low body mass index to be associated with osteoporosis as defined by densitometry. It is concluded that there are major differences between BMD values in European population samples which, with variations in anthropometric variables, have the potential to contribute substantially to variations in rates of osteoporotic fracture risk in Europe.

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Introduction

In Europe, there are great geographic variations in rates of osteoporotic fracture. The MEDOS study, a case–control study of hip fracture in southern Europe, demonstrated rates that in some age groups varied geographically by more than an order of magnitude [1]. Also, we have recently shown in the European Vertebral Osteoporosis (EVOS) study that vertebral deformities vary over a 3-fold range in both sexes [2,3]. EVOS was a prevalence study of 17342 male and female subjects drawn randomly from local populations registers. All were between 50 and 80 years of age and each population sample was age stratified.

Of the 36 participating EVOS centres, 13 took the opportunity to make bone mineral density (BMD) measurements of the spine and/or hip region using dual-energy X-ray absorptiometry (DXA) equipment. An additional three centres joined the present study because they had used identical principles to recruit their subjects, although they did not take lateral spine X-ray films at the same time. An important objective of doing this was to see whether BMD varied between populations and, if so, whether these variations were sufficient in scale and direction to account for a proportion at least of fracture rate variation in Europe. Because the EVOS centres have used densitometers made by different manufacturers, it was important first to cross-calibrate the measurements obtained. An approach to doing this using the European Spine Phantom (ESP) and its predecessor the ESP prototype (ESPp) has recently been published [4–6]. We have found substantial differences in BMD between populations that cannot be accounted for by variations in height, weight or selection bias.

Materials and Methods

Populations

Sixteen centres in 12 countries took part in the study (Table 1), 13 of them being centres participating in EVOS. In EVOS each centre used a population-based register from their locality to select a population-based random sample of up to 600 subjects. As previously described, each sample was stratified equally by sex and age into six 5-year age bands (50–54, 55–59, 60–64, 65–69, 70–74, 75–80) and the mean response rate was 54% in EVOS as a whole and 60% in the 13 EVOS centres represented in this study [2,3]. In each of these 13 EVOS centres, random subsamples of between 20% and 100% of recruited subjects were invited for bone densitometry. In Harrow, the subsample was a true random sample of the main sample, while in the other centres attempts were also made to ensure that the densitometry subsample was free of selection bias. The subjects from Cambridge [7] and Malmö [8] were drawn randomly from the subjects measured in these non-EVOS studies according to the same principles used in EVOS. Manchester recruited for their COMAC-BME centre [4,6] according to the principles used in EVOS as outlined above. All centres performed densitometry of the lumbar spine, and 14 centres performed densitometry of the hip. Altogether, 4774 complete records on the spine were received (2555 women) and 3826 records on the hip (2089 women). The number of subjects per centre varied from 71 to 517, with a median of 313. In the 13 EVOS centres, all participating subjects had a lateral radiograph, which was evaluated in Berlin for the presence of one or more vertebral deformities.

Table 1. Densitometer brand and numbers of subjects from each centre

Densitometer brand	Centre	Sex		
		Male	Female	All
Hologic	Berlin	194	176	370
	Heidelberg	106	85	191
	Harrow	35	36	71
	Moscow	72	111	183
	Oviedo	230	256	486
	Cambridge	155	276	431
Lunar	Leuven	131	190	321
	Rotterdam	240	242	482
	Manchester	24	50	74
	Oslo	146	158	304
	Malmö	84	95	179
	Erfurt	96	122	218
Sopha	Graz	266	248	514
Norland	Budapest	165	196	361
	Aberdeen	260	257	517
	Piestany	24	83	107
All		2228	2581	4809

DXA and Cross-Calibration

The densitometers in each centre were cross-calibrated using the ESPp. In previous work we found that the L2–4 region of the spine [6] as well as the femoral neck and trochanter [4] could be satisfactorily cross-calibrated for Hologic, Lunar and Norland pencil beam machines. Appendix A gives our method for cross-calibrating the Sopha machine in this study. The ESPp is a semi-anthropomorphic phantom with three "vertebrae" of specified densities: 0.5 g/cm^2, 1 g/cm^2 and 1.5 g/cm^2. At least five measurements of the phantom were made on each machine and a two-parameter exponential model fitted:

$$y = \alpha(1 - e^{-\beta x}) \quad (1)$$

where y is measured density and x is specified density, as described by Pearson et al. [5]. All bone density measurements were then converted to standardized densities using Eq. (1) rearranged as in Eq. (2) and using the values of a and b specific to the centre's densitometer:

$$\text{Standardized density} = \frac{-\log\left(1 - \frac{y}{\alpha}\right)}{\beta} \qquad (2)$$

DXA Quality Control

All centres participated in one or both of the following EU Concerted Actions: "Quantitative Assessment of Osteoporosis" (COMAC-BME, Project Coordinator J. Dequeker) and EVOS (Project Coordinator A. J. Silman). Each Concerted Action organized annual meetings at which principles and procedures for performing densitometry and densitometric analyses according to the manufacturer's instructions were agreed and monitored. Quality control in densitometry was enhanced by regular visits to centres by members of the two project management groups and periodic review of specimen analyses. Also, outlier values were identified, queried and, if appropriate, re-analysed by the centres. Day-to-day quality control was managed by the centres, which ensured machine stability by performing calibrations with their machine-specific phantoms daily or every other day. Patient positioning was carried out using the instructions and accessories of the manufacturers. All Lunar centres rigorously excluded the small numbers of scans in which air had inadvertently been scanned by inadequate "bolusing" of the hip region. The principal residual scope for between-centre systematic differences lay in possibly different approaches to editing of lateral spine edges. This editing process was therefore proscribed by agreement between all centres so as to minimize between-centre variation in technique.

Statistics

The dependent variables investigated were the means and variances of the standardized bone densities for each of the three measured sites: spine, femoral neck and femoral trochanter. For each dependent variable the aims were: (i) to see how it varied with age, height, weight and centre; (ii) to test for significant differences between centres; (iii) to test whether the effects of age, height and weight differed between the different centres.

Means. ANOVA was used to test for differences between centres in crude means, for each sex separately. The correlation between bone density at the three different sites was measured in each centre, and differences between centres in the relationships between densities at different sites tested using linear regression, including centre as a covariate.

To investigate the effects of age, height and weight on bone density, first a "comprehensive" model was established, fitting bone density to age, height, weight, measurement centre and all interactions of age, height and weight with centre. To allow for possible non-linearity in the relationship between age and bone density, age^2 and its interaction with centre were also fitted. In preliminary testing it was established that there was no measureable non-linearity in the relationships between bone density and any of the other variables. As the normality of the residuals improved after log-transformation, all subsequent analyses were based on the log of bone density. After transformation there was a very small number of outliers (<3 per sex per site), which were not excluded from the analysis since they did not affect the parameter estimates. Then a backwards step-wise approach was used to remove variables from the model that were not significant predictors (at $p = 0.05$). Where a p value is quoted for an effect it represents the p value in the final model, or the p value in the last model before it was removed. Separate final models for each sex and site were produced.

There was evidence that the variance in bone density increased with age, contrary to the assumptions of normal errors multiple regression. If uncorrected, this would lead to inaccurate hypothesis tests for between-centre comparisons. An iteratively reweighted least squares (IRLS) method due to Aitkin [9] was therefore used to correct for this, implemented as an SAS macro [10]. This method will also correct for any possible difference in variance between centres.

The variances due to differences between centres were each assumed to be the sums of two components in each case: variance between manufacturer's brands and remaining variance between centres. These components were compared using an F-test to see whether the differences between brands were greater than would be expected given the observed differences between centres.

To test whether adjusting for age, height and weight reduced the differences in means between centres, the variance of the unadjusted centre means was compared with the variance of the centre means adjusted to age 65 years, height 1.65 m and weight 70 kg, using Pitman's test [11] for correlated variances.

Based on a study of a West African population, Asprey et al. [12] found a significant relationship between the ratio of sitting to standing height and BMD measurements in the spine or femoral neck. Although none of our centres measured sitting height, 12 of the 16 centres measured armspan. It seemed reasonable to use armspan as a means of investigating the possible relationship between body proportions and BMD in Europeans, since armspan and leg length are strongly correlated and leg length as a proportion of total height is complementary to sitting height. Therefore, having completed the modelling described above, the effect of armspan was investigated by taking the bone density model derived from all 16 centres and adding in armspan and height separately as independent variables in modelling the data from the 12 centres, and finally adding in both together.

Standard Deviations. Differences between centres in the standard deviation of the distribution of bone density

could not be tested for directly, since the distributions were not normal, and testing for differences in standard deviation requires normality. A log-transformation would have normalized the data, but the variance of the transformed data in each centre would then have depended on the mean value in that centre, which would affect any test of differences in variance. To avoid this problem, the appropriate centre- and sex-specific mean value was subtracted from each measurement so that the mean value in each centre became 0. A constant was then added to each term to ensure that all values were positive, then the data were log transformed. These "residuals" could then be tested for differences in standard deviation (strictly differences in variance, the square of the standard deviation) using Bartlett's test [11].

To test whether there were significant between-centre differences in standard deviation after adjusting bone density for age, height and weight, the residuals from the final regression model were used. Bartlett's test could be applied to these directly, since they were already normally distributed.

There were considerable differences in the numbers of subjects from each centre. This would not bias the results, provided there was no bias in the selection of subjects, since centres with few subjects will have less effect on the regression model than centres with many subjects. However, in a given centre, if subjects with low bone density were more or less likely to be measured than subjects with high bone density, this would affect the estimate of mean bone density in that centre. If any demonstrable selection bias differed between centres, this could create apparent differences between centres when the true mean bone density was the same. If the relative risk of subjects with low bone density attending for densitometry varied with age then the regression coefficients for the effect of age on bone density would be biased. If this effect differed between centres, it would explain differences in apparent rates of bone loss between centres.

It is not possible to test directly whether such selection bias did occur, since we do not know the bone density of the subjects who were not measured. However, all EVOS subjects underwent a lateral spinal radiograph. These were evaluated quantitatively in Berlin for the presence of vertebral deformities. We used these deformity data as surrogate measures, assuming that subjects with deformities were more likely to have low bone density [13]. The relative risk of receiving densitometry in subjects with vertebral deformities compared with subjects without deformities was calculated using the Mantel Haenszel method, to assess the overall selection bias. To test for differences between centres in the relative risk, the Breslow-Day test [14] for homogeneity for the odds ratios was used. Logistic regression was used to determine whether the probability of subjects with low bone density attending for densitometry varied with age, and whether this effect differed between centres.

Results

Mean Bone Density Values

There were highly significant differences between centres in mean bone density. Adjusting for age, height and weight had very little impact on these differences; the significance level of the differences did not change greatly ($p < 10^{-4}$ for all sites, for both sexes, before and after adjustment) and the between-centre variance was not significantly reduced ($p > 0.15$ for all sites and both sexes). The between-centre standard deviation was approximately one-quarter of the between-subject standard deviation, i.e. the difference in mean bone density between the highest and lowest centres was about 1 population SD (Tables 2, 3). Figure 1 shows the mean values at each centre for all three measurements sites adjusted for weight and age. Figure 2 shows individual data from the trochanter and spine to illustrate the effects of centre-related differences in relation to age.

Table 2. Means and standard deviations of standardized, crude bone density values for both sexes in 16 European centres (results expressed in g/cm^2)

Centre	Spinal bone density		Trochanteric bone density		Femoral neck bone density	
	Mean	SD	Mean	SD	Mean	SD
Women						
Aberdeen	0.9585	0.1911	0.6820	0.1292	0.8038	0.1386
Berlin	1.0670	0.2367	0.7070	0.1240	0.8317	0.1555
Budapest	0.9349	0.1599	0.7068	0.1189	0.8286	0.1245
Erfurt	1.0023	0.2299				
Graz	0.9624	0.2252				
Harrow	1.0637	0.2592	0.6944	0.1516	0.8117	0.1774
Heidelberg	1.0934	0.2489	0.6988	0.1554	0.7921	0.1486
Cambridge	1.0844	0.2406	0.6701	0.1285	0.7506	0.1422
Leuven	1.0000	0.2118	0.6882	0.1432	0.7698	0.1421
Malmö	0.9396	0.1836	0.6500	0.1462	0.7304	0.1519
Manchester	1.0327	0.2015	0.6928	0.1168	0.7938	0.1187
Moscow	1.0489	0.2335	0.6812	0.1229	0.8045	0.1624
Oslo	0.9364	0.1852	0.6463	0.1385	0.7235	0.1348
Oviedo	0.9585	0.2152	0.6070	0.1042	0.7347	0.1306
Piestany	0.9396	0.1509	0.6860	0.1062	0.8132	0.1123
Rotterdam	0.9790	0.1932	0.6733	0.1330	0.7667	0.1273
Men						
Aberdeen	1.1419	0.2026	0.8898	0.1268	0.9134	0.1358
Berlin	1.1739	0.2126	0.8239	0.1400	0.9033	0.1437
Budapest	1.0473	0.1688	0.8431	0.1096	0.9094	0.1129
Erfurt	1.1048	0.1857				
Graz	1.1000	0.2465				
Harrow	1.2337	0.2429	0.8361	0.1417	0.9123	0.1767
Heidelberg	1.2621	0.3082	0.8506	0.1471	0.9252	0.1792
Cambridge	1.2128	0.2780	0.7920	0.1547	0.8296	0.1591
Leuven	1.1098	0.2138	0.8329	0.1565	0.8620	0.1584
Malmö	1.1179	0.2059	0.8497	0.1589	0.8653	0.1397
Manchester	1.1680	0.1920	0.8504	0.1210	0.8942	0.1439
Moscow	1.1880	0.2478	0.7775	0.1340	0.8940	0.1486
Oslo	1.0660	0.1974	0.8237	0.1412	0.8589	0.1245
Oviedo	1.1525	0.2424	0.7700	0.1369	0.8831	0.1656
Piestany	1.1433	0.2012	0.8517	0.1245	0.9179	0.1044
Rotterdam	1.1379	0.2200	0.8161	0.1388	0.8520	0.1307

Table 3. Comparison of unadjusted with adjusted[a] mean standardized bone density values (results expressed in g/cm^2) and the effect of adjustment on population and between-centre standard deviations

	Men			Women		
	Spine	Trochanter	Femoral neck	Spine	Trochanter	Femoral neck
Mean bone density						
Crude	1.138	0.827	0.885	0.993	0.674	0.780
Adjusted	1.056	0.784	0.842	0.959	0.661	0.761
Population SD						
Crude	0.2318	0.1426	0.1485	0.2169	0.1309	0.1430
Residual	0.2204	0.1334	0.1355	0.1926	0.1068	0.1194
Between-centre SD						
Crude centre means	0.0582	0.0323	0.0291	0.0570	0.0366	0.0273
Adjusted centre means	0.0566	0.0309	0.0357	0.0507	0.0244	0.0286
Crude between-centre SD/crude population SD	25%	23%	20%	26%	28%	19%
Adjusted between-centre SD/residual SD	26%	23%	26%	26%	23%	24%

[a]Adjusted to age 65 years, weight 70 kg, height 1.65 m.

Effect of Machine Brand. After cross-calibration there were still differences in mean bone density between densitometers of different brands, at the femoral neck and spine in both sexes. The mean bone density at each site, after adjusting for age, height and weight, for each brand of densitometer is given in Table 4. The differences between centres after adjusting for instrument brand (which makes the assumption that there is no true difference between populations means used by different brands of densitometer) remained highly significant ($p<10^{-2}$ at the femoral neck in men; $p<10^{-3}$ at all other sites). As Table 4 shows, there were significant differences between centres using the same brand of densitometer when all three brands of densitometer were considered separately, showing that the between-centre differences are not due to inadequate cross-calibration between brands.

Effects of Other Variables

The final regression models for all sites and both sexes for the bone density means and variances are given as algebraic equations in Appendices B and C. The statistical significance of the various differences between centres are summarized in Table 5. Appendices B and C give regression equations for each sex and BMD site, by centre, with age, age^2, weight and height as the independent variates. The effects that were common to all centres are given below.

Effect of Age. For women, there was considerable curvature in the relationship between age and bone density at all three sites ($p<0.002$), with the rate of decrease of bone density tending to decrease with age. At the femoral neck, relationships with age were similar in each centre: on average bone density decreased by 1.23% per year at age 55 years, 0.77% per year at age 65 years, and by 0.31% per year at age 75 years. At the spine and trochanter, the rate of bone loss at age 65 years varied between centres (see Appendix B, Tables B1 and B2 for details).

In men, the effects of age was less strong than in women. At the femoral neck and trochanter there was no evidence of differences between centres with age in rates of change or in curvature ($p>0.2$). Bone density did not change significantly with age at the trochanter (estimate 0.08% per year; 95% CI: −0.16%, 0.01%) and decreased at a constant rate of 0.25% per year at the femoral neck (95% CI: 0.16%, 0.34%).

At the spine in men, there was evidence of differences between centres in rate of change at age 65 years ($p=0.03$), but the curvature in the relationship of density with age was slight and similar between centres. Bone density decreased significantly with age in one centre (Leuven), increased significantly in seven centres, and was not significantly different from zero in seven centres (Appendix B, Tables B4–B6).

Effect of Weight. In men, the effect of weight on bone density was consistent between sites and centres. Bone density increased by 0.52% for every kilogram increase in weight at the spine, 0.53% per kg at the trochanter, and by 0.51% for every kilogram increase at the femoral neck. In females, femoral neck bone density increased by 0.57% for every kilogram in all centres, but the effect of weight on bone density differed between centres at the spine and trochanter over 2- to 3-fold range (Appendix B, Tables B1 and B2).

Effect of Height. In men, height had no consistent effect on bone density at any site. The effect appeared to differ between centres at the femoral neck ($p=0.008$), due to a large positive effect in one centre (Manchester, density increased by 0.83% per cm) and a negative effect in one other centre (Rotterdam, density decreased by 0.43% per cm).

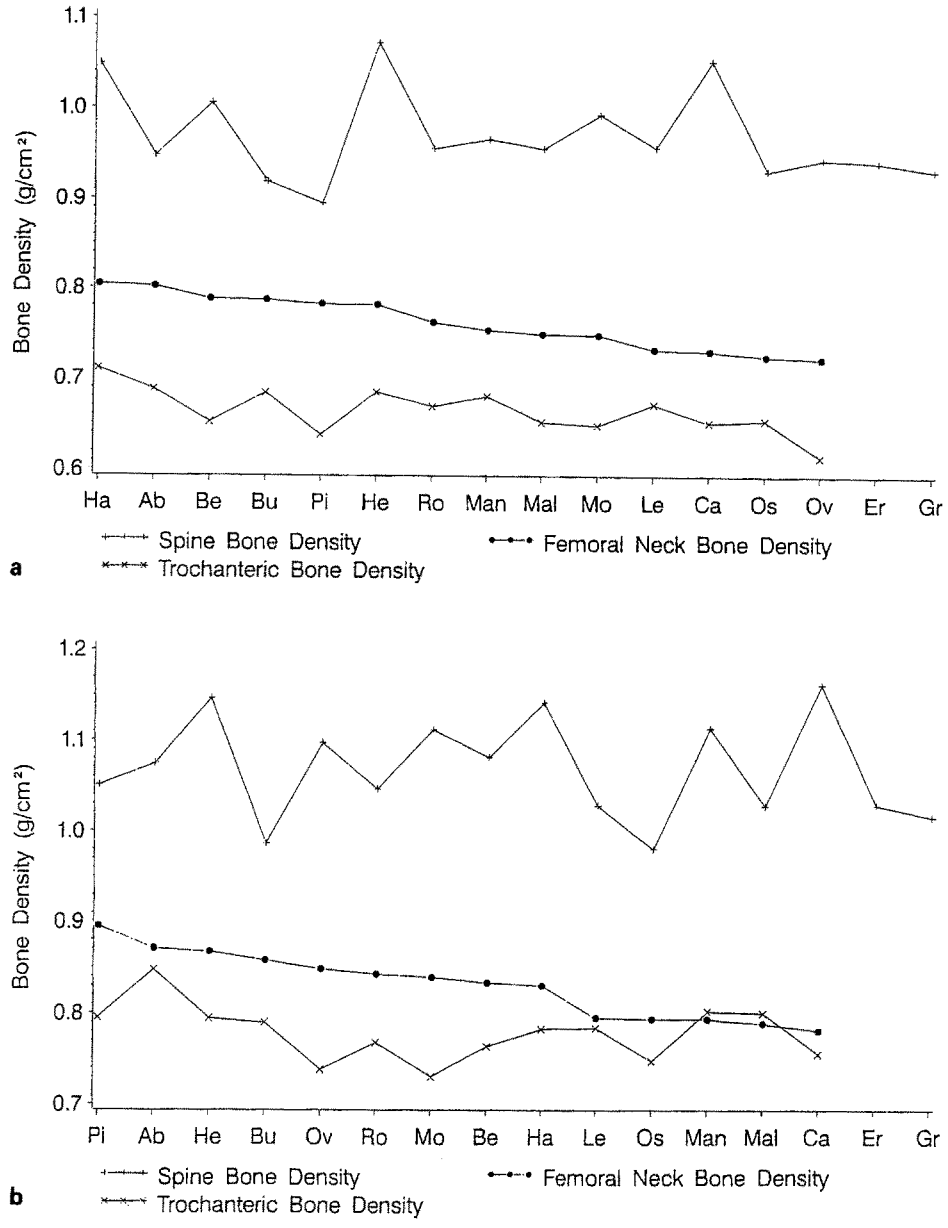

Fig. 1. Mean bone density at the spine, femoral neck and trochanter in each centre, after adjusting to age 65 years, height 1.65 m and weight 70 kg in women (**a**) and men (**b**). Centres are listed in order of decreasing femoral neck bone density. Ab, Aberdeen (UK); Be, Berlin (Germany); Bu, Budapest (Hungary); Ca, Cambridge (UK); Er, Erfurt (Germany); Gr, Graz (Austria); Ha, Harrow (UK); He, Heidelberg (Germany); Le, Leuven (Belgium); Mal, Malmö (Sweden); Man, Manchester (UK); Mo, Moscow (Russia); Os, Oslo (Norway); Ov, Oviedo (Spain); Pi, Piestany (Slovakia); Ro, Rotterdam (Netherlands).

In women there was no relationship between height and bone density at the trochanter or femoral neck ($p=0.23$, 0.4 respectively). At the spine, bone density increased by 0.16% for each centimetre increase in height, with no apparent differences between centres.

Effect of Armspan. In men from the centres that measured armspan, bone density increased slightly with increasing height (0.14% per cm) but was not associated with armspan (decrease of 0.07% per cm, $p=0.26$). However, when both armspan and height were included in the model, the association between height and bone density was stronger (increasing by 0.38% per cm) and armspan also became significant (decrease of 0.29% per cm, $p<0.0008$). In women from these centres, spine bone density was significantly associated with height (increase of 0.21% per cm) but not with armspan ($p = 0.19$). However, when both height and armspan were included, armspan remained non-significant ($p = 0.19$), while the effect of height increased slightly (increase of 0.30% per cm).

Trochanteric bone density decreased with increasing armspan in men. Bone density decreased by 0.19% per cm increase in armspan without adjusting for height, or

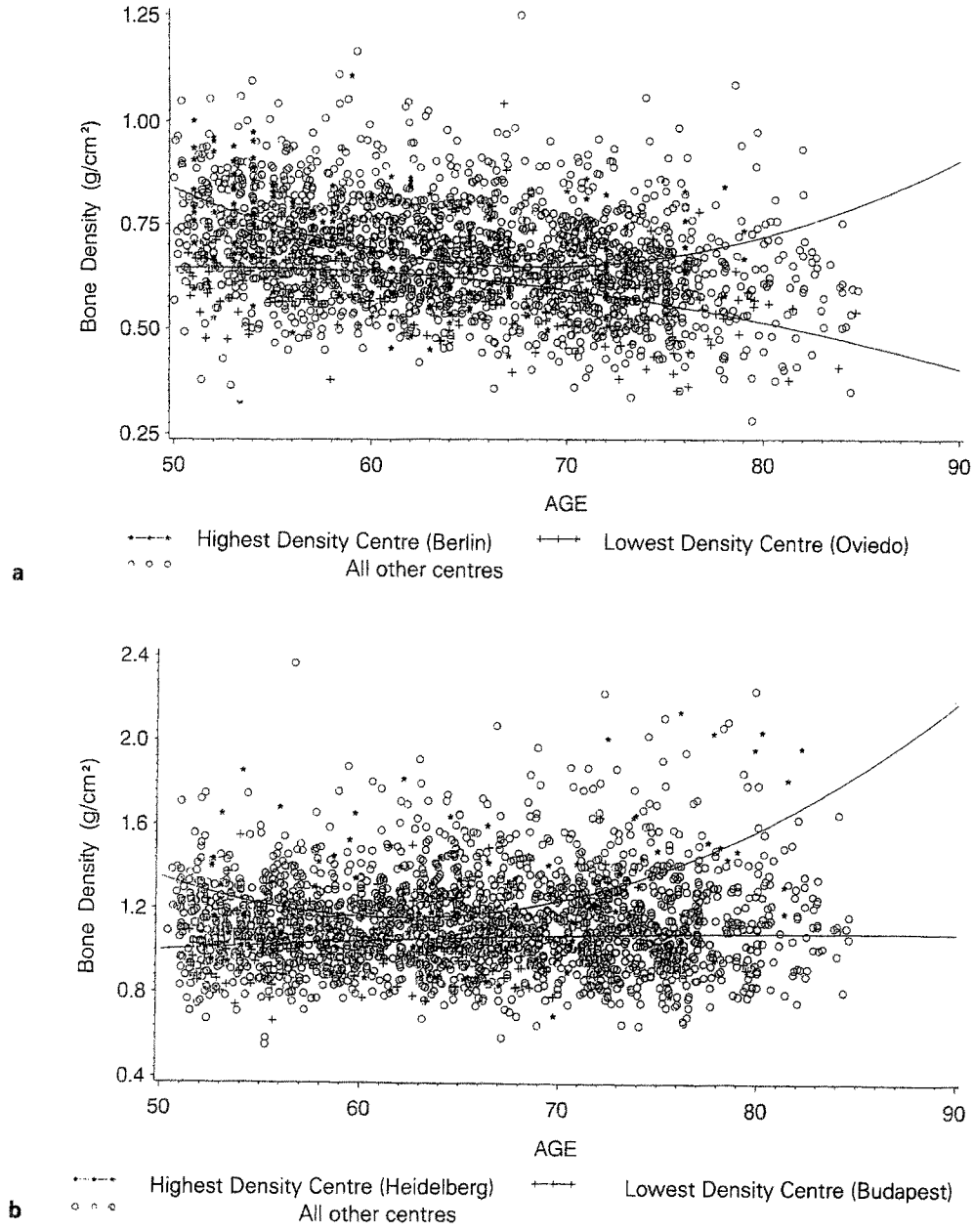

Fig. 2. Unadjusted individual results for trochanteric bone density in women (**a**) and spinal bone density in men (**b**), highlighting the results from the centres with the highest and lowest mean bone density. The regressions of bone density versus age for these highest and lowest centres are also shown.

0.24% with height adjustment, although height was not associated with bone density whether or not armspan was included in the model ($p > 0.1$). Neither height nor armspan had an association that was statistically significant with femoral neck bone density in either sex, nor at the trochanter in women ($p > 0.14$).

Between-Site Correlations. There were, as expected, relationships between the bone density at the femoral neck and the bone density at the trochanter ($r = 0.79$ in men, 0.79 in women, $p < 10^{-4}$ in both sexes). In addition, there were significant differences between centres in this relationship: allowing for between-centre differences increased the proportion of the variance in femoral neck bone density explained from 62% to 66% in men ($p < 10^{-4}$), and from 63% to 66% in women ($p = 0.001$). The relationship between bone density at the spine and at the trochanter was less strong ($R = 0.57$ in men, 0.63 in women; $p < 10^{-4}$ in both sexes). Again, the relationship varied significantly between centres: allowing for between-centre differences increased the proportion of the variance in spine bone density explained from 32% to 41% in men ($p < 10^{-4}$), and from 40% to 49% in women ($p < 10^{-4}$).

Table 4. Mean adjusted, standardized bone density by densitometer brand and significance of between-brand differences

	Mean bone densities			Significance of between-centre differences		
	Spine	Femoral neck	Trochanter	Spine	Femoral neck	Trochanter
Men						
Mean bone densities						
Hologic	1.186	0.873	0.795	0.03	0.01	0.002
Lunar	1.096	0.841	0.816	0.002	0.12	0.087
Norland	1.094	0.916	0.848	0.0001	0.47	0.0001
Sopha	1.074					
Signicance of differences between brands	0.025	0.048	0.099			
Women						
Mean bone densities						
Hologic	1.027	0.770	0.663	0.0001	0.0001	0.0002
Lunar	0.959	0.753	0.669	0.74	0.040	0.81
Norland	0.928	0.799	0.673	0.01	0.39	0.018
Sopha	0.942					
Signicance of differences between brands	0.013	0.059	0.85			

Table 5. Table of significance of differences between centres (probability values p tested against the null hypothesis) after adjusting for densitometer brand

Mean densities	Women			Men		
	Spine	Trochanter	Femoral neck	Spine	Trochanter	Femoral neck
Stanardized to age 65 years	<0.0001	0.0001	<0.0001	<0.0001	<0.0001	0.001
Rate of change with age at 65 years	0.02	0.51	0.46	0.03	0.40	0.23
Curvature in rate of change with age	0.77	0.005	0.89	0.23	0.72	0.46
Effect of weight	0.05	<0.0001	0.09	0.56	0.56	0.24
Effect of height	0.33	0.59	0.46	0.40	0.16	0.008

Potential Selection Bias

In women, there was no evidence that the subjects without vertebral deformities were more likely to receive bone densitometry (relative risk 1.05; 95% CI: 0.98, 1.12), nor of differences between centres (p = 0.14). In both Budapest and Heidelberg, women with deformities were less likely to have had densitometry, and so the mean bone densities of the populations in these centres could possibly be overestimated. However, Table 2 shows that Budapest has the lowest spinal bone density, although it has comparatively high hip bone density. Heidelberg ranked quite highly for both spine and trochanter, although not for femoral neck.

Older women were less likely to attend for bone densitometry than younger women, so any analyses need to be adjusted for age. However, there was no evidence that the probability that a subject with a deformity receiving bone densitmetry was affected by age overall (p = 0.7), nor that such an effect differed between centres (p = 0.12), so the estimates of the effect of age on bone density should be reliable.

In men, there was no evidence of selection bias overall (relative risk 1.05; 95% CI: 0.98, 1.13); however, there was a suggestion of differences between centres (p = 0.08). There were significant effects in Moscow and Oslo, where men with deformities were less likely to have had densitometry, and so the mean bone densities of these samples can be expected to be an overestimate of the mean bone densities in the relevant populations. However, Table 2 shows that neither of these centres has particularly high bone densities, Oslo being a centre with one of the lowest bone densities. Other than in these two centres, there is no evidence of selection bias either overall or differing between centres. Thus the observed differences in mean bone density between centres cannot be explained by selection bias.

In men, it appeared there were differences between centres in the association between age and the probability that a subject received densitometry (p = 0.02). However, this effect could be isolated to a single centre (Erfurt) where older subjects with deformities were more likely to be measured than younger subjects with deformities, so the rate of bone loss in this centre may be overestimated. However, only the spine was measured in this centre and Table B4 shows that while this centre showed a slower increase with age than most other centres, there were two centres

that showed an actual decrease in bone density with age. Other than at this centre, there was no evidence that the probability of a subject with a deformity receiving bone densitometry was affected by age overall ($p = 0.4$), nor that such an effect differed between centres ($p = 0.21$).

Standard Deviation (SD)

The SDs of the transformed densities differed significantly between centres, both before and after adjustment for height (which did not appear to affect the SD) and weight. In Appendix C, Tables C1–C6 give the SD of the bone density in each centre at each site for each sex, adjusted to age 65 years and weight 70 kg.

Effect of Age. In men, the SD of the bone density increased with increasing age by 0.77% for each additional year at the spine (95% CI: 0.41%, 1.14%), 0.48% at the trochanter (95% CI: 0.07%, 0.89%), and 0.57% at the femoral neck (95% CI 0.17%, 0.98%). This effect did not appear to differ between centres.

In women, age did not appear to affect the SD of bone density at the femoral neck. However, the SD increased with each year of age by 1.18% at the spine (95% CI: 0.84%, 1.52%), and by 0.55% at the trochanter (95% CI: 0.17%, 0.93%).

Effect of Weight. In women, the SD of hip bone density was inversely related to weight, decreasing as weight increased. The decreases were very similar at the neck and trochanter: −0.38% (−0.65%, −0.12%) per kilogram weight increase at the femoral neck and −0.44% (−0.70%, −0.17%) per kilogram weight increase at the trochanter. The combined effects of weight on bone density and bone density SD in two populations of women – those with respectively the highest and lowest mean femoral neck adjusted bone density values – are illustrated in Fig. 3. This shows the prevalence of bone density values below a cut-off of 2.5 SDs below the mean young normal value reported in a mixed European population by Pearson et al. [4].

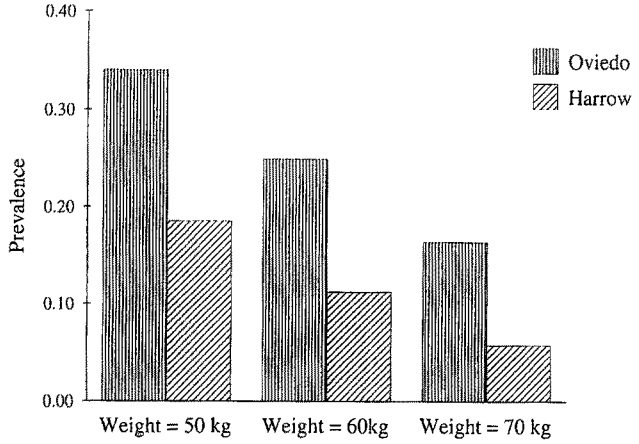

Fig. 3. Predicted prevalence of female femoral neck bone density values below 0.580 g/cm^2 after adjustment to age 65 years according to our statistical model. This is the value presented by Pearson et al. [4] for a mixed population of normal young European women to represent a *T*-score of −2.5 as defined by Kanis et al. [34]. For illustrative purposes, women are considered from our two centres with the highest (Harrow) and lowest (Oviedo) mean age- and weight-adjusted BMD values in the femoral neck; both these centres used Hologic machines. The predicted prevalences among women of 50 kg, 60 kg and 70 kg body weight are shown to demonstrate the association of low bone density with low body weight.

Discussion

These results have demonstrated clear differences between European populations in bone density at all three sites measured. These are evident between centres using the same brand of densitometer and persisted after cross-calibration and additional statistical adjustments for machine brand, so cannot be considered possible artefacts due to cross-calibration errors. Variations in body size have also been documented but these explain only a small part of the differences in bone density. Comparison of our data with those obtained in a multicentre study performed in the continental USA suggests that on a geographical basis bone density variation in Caucasians is several-fold larger in Europe than in North America [15]. In fact, for the female femoral neck data, the mean difference between Oviedo (the lowest) and Harrow (the highest) suggests a difference in future hip fracture risk of 2.5- to 3.0-fold based on the relationship established by Cummings et al. [16] (Incidentally, both of these centres used Hologic densitometers.) The results presented in this paper offer no explanation for the observed variations in bone density. It is likely that these are the results of interactions between genetic and environmental factors.

Previous studies comparing Caucasian populations with those of other ethnic origins have found substantial between-group differences in BMD [17–21], but this is the first study which has shown in true population samples substantial differences in BMD between different Caucasian populations, after adjusting for body size.

Since our early publications on the ESPp [4–6], it has now been established that this is not a perfect instrument for cross-calibrating different manufacturers' brands of bone densitometer. In particular, since the development of an improved ESP [6,22] it has now become clear that use of the ESPp leads to modest overestimates of standardized values measured in the spine by Hologic machines. This is probably the indirect result of underestimates of the bone density by Hologic machines when measuring the 1.5 gm/cm^2 "vertebra" in the ESPp by comparison with the definitive version of the ESP. Realizing this problem, we applied a statistical approach to adjust for potential systematic errors in cross-calibration.

Possibly because of the size of the populations studied or because of the recruitment method whereby subjects were not excluded who might have been excluded from other so-called normal series, we have identified certain

statitical characteristics of our data which have only been noted inconsistently in the previous literature. The trend towards log-normality of data distribution is noteworthy. This confirms observations made in the previous COMAC-BME study for the majority of sites measured in the DXA data series [4,6]. The change in variance with age is another notable aspect of our results. With respect to the spine measurements it seems possible that this could relate to the impact of spinal osteoarthritis as noted previously by Masud et al. [23] and Burger et al. [24]. The differences between centres in trends with age and the effect of age on variance were previously commented on in the COMAC-BME study, but that study was not consistent in the recruitment method used. The present study, which is considerably larger, has established that both characteristics of European multicentre DXA data are intrinsic to the populations rather than the result of methodological inconsistency. The COMAC-BME centres which based their recruitment on random samples of their local populations have also joined the present study, so some of the present data from Berlin, Harrow, Leuven, Manchester and (with a 50% sample) Aberdeen have also been included in the two relevant COMAC-BME publications [4,6]. For logistic and financial reasons, it was not possible to attempt to recruit population samples that were representative of the national populations from which the subjects came. Therefore, our samples are representative of their local populations, not necessarily of their national populations.

These measurements were all performed at the beginning of a prospective study of osteoporotic fracture based on normal European populations [25] – now known as the European Prospective Osteoporosis Study. Currently it is not known whether variations in bone density in these populations will translate into similar variations in incident fractures. In previous single-country European [26,27] and North American [16,28,29] studies, bone density has been shown to be predictive of fracture in age groups ranging over the spread of ages studied in the populations represented in this paper. However, components of fracture risk not attributable to bone density have been identified by Ross et al. [30,31] and others in patients who have suffered a previous osteoporotic fracture. It has now been shown in several studies that the existence of a prevalent fracture is a risk factor for a further osteoporotic fracture at the same or another site, which at any given level of bone density is significantly higher than for controls matched for bone density but not having suffered a previous (prevalent) deformity [30,31]. Vertebral dimensions also contribute to risk [32]. It is therefore plausible that variations in bone density in Europe will not translate into comparable variations in fracture incidence because of other elements of fracture risk which are not captured by DXA measurements. Before substantial resources are directed towards using bone density measurements as surrogates for risk measurement which can be exported between communities, further work needs to be done to compare relationships in different communities between bone density and fractures. For example, we already know that fracture rates in some African countries [21,33] and among the Maoris of New Zealand [20] may not be entirely explained by the risk models based on relationships observed between BMD and fracture risk in Caucasian populations.

In previous epidemiological work in Europe, hip fracture risk has been shown to have a high degree of geographic variability in the MEDOS study, with the oldest cohorts in the least-affected centre having a 13-fold lower risk than comparable cohorts in the most-affected centre [1]. It seems unlikely from the data presented that such a spread on fracture risk could be accounted for solely by bone density on relationships previously published between incident fracture rates and bone density levels. However, the 3-fold variation in vertebral deformity prevalence reported by O'Neill et al. [3] is within the range that might be explained by bone density variation in Europe.

For the management of female patients at risk of osteoporosis, the WHO [34] has recently suggested that for those under 75 years their bone density should be assessed in relation to the distribution of values obtained in young normal subjects. Our results raise several questions in relation to this proposal. The first is whether young normal subjects from different European communities will show the same variation in bone density as obtained in our subjects over the age of 50 years. If this is the case the question then arises whether risk assessment should be related to young normal values obtained in the local community or to some composite normal value obtained by pooling results from many communities. This in turn reflects back on the question of whether absolute values of bone density in Europe are more closely related to risk of incident fractures than some locally derived index of deviation from the young normal standard. The collection of adequate amounts of young normal data to provided local standards for risk assessment will be a daunting task in some countries, because the precise definition of standard deviation in terms of a defined level of methodological precision requires larger numbers than the definition of mean values to the equivalent level of precision. There is also the problem with young subjects of ensuring representative sampling because of high refusal rates among recruits experienced in many countries when representative samples are sought based on the population registers.

In conclusion, our study has demonstrated substantial variations between European populations in mean bone density, the variance of bone density and rates of change with age in populations. These variations are not explained by differences in body size and may have considerable implications for explaining variations in fracture rate already documented across Europe. Our results are also relevant to implementing the recommendations of the WHO for using bone densitometry in fracture risk assessment in patients. We conclude that it is important to document the relationship between risk of incident fractures and bone density in the populations we

have studied. The EVOS prevalence study has now become the European Prospective Osteoporosis Study (EPOS) of incident fractures, which has been in progress for 3 years and is still continuing. We are therefore enlarging our database of DXA measurements performed in the centres contributing to EPOS with an additional 10 or more centres planning to perform bone densitometry for use in prospective risk assessment.

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Appendices

Appendix A. Cross-Calibration of the Sopha SRA Fan-Beam Densitometer (Graz)

The Sopha SRA fan-beam densitometer was supplied by the manufacturer with an aluminium alloy phantom cut out of sheet metal as well as a Perspex "water-equivalent" block on the top of which this manufacturer's phantom is scanned for daily quality control. This block was exactly the same height as the ESPp. After early attempts to scan the ESPp had failed, due to the densitometer's software failing to define the edges of the three ESP "vertebrae", it was found that this problem was easily rectified by scanning the Perspex block without the manufacturer's phantom and the ESPp placed together on the couch, allowing no air gap between them. The scan was begun in the block and continued into the phantom for a distance of two vertebrae. Results for the central vertebra were near-identical whichever way round the ESPp was scanned. As with all the DXA machines in the study, imaged ESPp vertebral edges were machine defined and operator editing was proscribed, the only allowable exceptions being re-definition of the intervertebral spaces if necessary.

Appendix B. Regression Models for Bone Density

The intercept represents the mean bone density in that centre at age 65 years, height 1.65 m and weight 70 kg. The values in the other columns are the percentage change in bone density per unit increase in that quantity. The 95% confidence intervals are given in parentheses. Units: age in years, height in cm, weight in kg, bone density in g/cm^2.

Appendix C. Regression Models for the Population Standard Deviation of Bone Density

The intercept represents the population standard deviation in bone density in that centre at age 65 years and weight 70 kg. The values in the other columns are the percentage change in bone density per unit change in that quantity. The 95% confidence intervals are given in parentheses.

Table B1. Spinal bone density: women

Centre	Intercept	Age	Age^2	Height	Weight
Aberdeen	0.947 (0.924, 0.972)	−0.67% (−0.91%, −0.43%)			0.41% (0.24%, 0.58%)
Berlin	1.005 (0.968, 1.043)	−0.63% (−1.04%, −0.22%)			0.49% (0.24%, 0.75%)
Budapest	0.919 (0.895, 0.944)	−0.01% (−0.30%, 0.29%)			0.92% (0.73%, 1.11%)
Erfurt	0.943 (0.907, 0.980)	−0.23% (−0.70%, 0.24%)			0.64% (0.36%, 0.91%)
Graz	0.934 (0.906, 0.962)	−0.61% (−0.92%, −0.29%)			0.51% (0.29%, 0.73%)
Harrow	1.048 (0.979, 1.123)	−0.80% (−1.61%, 0.02%)			0.71% (0.25%, 1.18%)
Heidelberg	1.071 (1.023, 1.122)	−0.45% (−1.03%, 0.14%)			0.54% (0.18%, 0.91%)
Cambridge	1.054 (1.026, 1.082)	−0.64% (−0.93%, −0.34%)	0.036% (0.025%, 0.046%)	0.16% (0.04%, 0.28%)	0.72% (0.53%, 0.92%)
Leuven	0.958 (0.930, 0.986)	−0.53% (−0.86%, −0.21%)			0.79% (0.58%, 1.01%)
Malmö	0.956 (0.918, 0.995)	−0.77% (−1.05%, −0.49%)			0.68% (0.36%, 1.01%)
Manchester	0.965 (0.906, 1.029)	−0.62% (−1.13%, −0.10%)			0.50% (0.03%, 0.99%)
Moscow	0.993 (0.952, 1.036)	−0.28% (−0.79%, 0.23%)			0.38% (0.10%, 0.66%)
Oslo	0.933 (0.907, 0.960)	−0.86% (−1.19%, −0.53%)			0.55% (0.31%, 0.79%)
Oviedo	0.946 (0.918, 0.974)	−0.59% (−0.86%, −0.31%)			0.70% (0.47%, 0.93%)
Piestany	0.895 (0.867, 0.923)	−0.17% (−0.55%, 0.22%)			0.65% (0.40%, 0.89%)
Rotterdam	0.955 (0.932, 0.979)	−0.42% (−0.73%, −0.10%)			0.65% (0.45%, 0.85%)

Table B2. Trochanteric bone density: women

Centre	Intercept	Age	Age^2	Weight
Aberdeen	0.688 (0.671, 0.706)		0.023% (0.001%, 0.046%)	0.79% (0.65%, 0.94%)
Berlin	0.652 (0.630, 0.674)		0.068% (0.034%, 0.101%)	0.39% (0.22%, 0.57%)
Budapest	0.684 (0.665, 0.703)		0.006% (−0.021%, 0.033%)	0.90% (0.71%, 1.09%)
Harrow	0.711 (0.656, 0.770)		−0.008% (−0.090%, 0.074%)	0.80% (0.42%, 1.19%)
Heidelberg	0.685 (0.646, 0.725)		0.027% (−0.046%, 0.100%)	0.71% (0.38%, 1.04%)
Cambridge	0.652 (0.634, 0.671)		0.027% (−0.004%, 0.058%)	0.62% (0.47%, 0.78%)
Leuven	0.672 (0.649, 0.696)	−0.62% (−0.71%, −0.52%)	−0.014% (−0.049%, 0.021%)	0.90% (0.69%, 1.12%)
Malmö	0.652 (0.617, 0.690)		0.046% (0.018%, 0.075%)	1.01% (0.65%, 1.37%)
Manchester	0.680 (0.646, 0.716)		0.003% (−0.024%, 0.030%)	0.71% (0.36%, 1.07%)
Moscow	0.649 (0.619, 0.680)		0.007% (−0.055%, 0.069%)	0.40% (0.17%, 0.62%)
Oslo	0.655 (0.612, 0.701)		0.044% (−0.071%, 0.080%)	0.93% (0.52%, 1.34%)
Oviedo	0.615 (0.600, 0.631)		0.013% (−0.037%, 0.011%)	0.63% (0.46%, 0.80%)
Piestany	0.638 (0.609, 0.669)		0.091% (0.027%, 0.155%)	0.39% (0.16%, 0.63%)
Rotterdam	0.669 (0.652, 0.686)		0.008% (−0.016%, 0.032%)	0.97% (0.80%, 1.15%)

Table B3. Femoral neck bone density: women

Centre	Intercept	Age	Age^2	Weight
Aberdeen	0.801 (0.787, 0.816)			
Berlin	0.788 (0.769, 0.807)			
Budapest	0.786 (0.773, 0.801)			
Harrow	0.804 (0.767, 0.843)			
Heidelberg	0.781 (0.756, 0.808)			
Cambridge	0.730 (0.717, 0.744)			
Leuven	0.732 (0.716, 0.749)	−0.77% (−0.85%, −0.70%)	0.023% (0.016%, 0.031%)	0.57% (0.52%, 0.62%)
Malmö	0.749 (0.724, 0.775)			
Manchester	0.753 (0.733, 0.773)			
Moscow	0.748 (0.726, 0.771)			
Oslo	0.725 (0.697, 0.754)			
Oviedo	0.723 (0.709, 0.737)			
Piestany	0.782 (0.761, 0.804)			
Rotterdam	0.762 (0.747, 0.777)			

Table B4. Spinal bone density: men

Centre	Intercept	Age	Age^2	Weight
Aberdeen	1.074 (1.051, 1.099)	0.27% (0.04%, 0.50%)		
Berlin	1.082 (1.052, 1.112)	0.31% (0.02%, 0.61%)		
Budapest	0.986 (0.958, 1.015)	0.34% (0.01%, 0.69%)		
Erfurt	1.030 (0.996, 1.065)	0.06% (−0.28%, 0.40%)		
Graz	1.017 (0.990, 1.045)	0.30% (0.00%, 0.60%)		
Harrow	1.143 (1.067, 1.224)	0.15% (−0.57%, 0.87%)		
Heidelberg	1.147 (1.100, 1.196)	0.83% (0.33%, 1.34%)		
Cambridge	1.163 (1.107, 1.222)	−0.49% (−1.25%, 0.27%)		
Leuven	1.029 (0.995, 1.063)	−0.35% (−0.69%, −0.01%)	0.011% (0.000%, 0.022%)	0.52% (0.45%, 0.59%)
Malmö	1.029 (0.989, 1.071)	0.15% (−0.18%, 0.49%)		
Manchester	1.115 (1.041, 1.193)	0.47% (−0.08%, 1.02%)		
Moscow	1.112 (1.065, 1.162)	0.46% (−0.12%, 1.04%)		
Oslo	0.981 (0.952, 1.011)	0.35% (0.00%, 0.70%)		
Oviedo	1.097 (1.068, 1.127)	0.34% (0.04%, 0.64%)		
Piestany	1.051 (0.992, 1.113)	0.86% (0.12%, 1.61%)		
Rotterdam	1.047 (1.021, 1.073)	0.31% (0.00%, 0.61%)		

Table B5. Trochanteric bone density: men

Centre	Intercept	Age	Weight
Aberdeen	0.848 (0.833, 0.862)		
Berlin	0.763 (0.745, 0.781)		
Budapest	0.789 (0.773, 0.805)		
Harrow	0.782 (0.742, 0.824)		
Heidelberg	0.794 (0.769, 0.820)		
Cambridge	0.755 (0.733, 0.777)		
Leuven	0.783 (0.759, 0.808)	−0.08% (−0.17%, 0.01%)	0.53% (0.47%, 0.60%)
Malmö	0.800 (0.771, 0.831)		
Manchester	0.802 (0.761, 0.846)		
Moscow	0.730 (0.704, 0.757)		
Oslo	0.747 (0.707, 0.789)		
Oviedo	0.738 (0.722, 0.754)		
Piestany	0.795 (0.759, 0.833)		
Rotterdam	0.767 (0.751, 0.784)		

Table B6. Femoral neck bone density: men

Centre	Intercept	Age	Height	Weight
Aberdeen	0.870 (0.850, 0.891)		0.03% (−0.24%, 0.29%)	
Berlin	0.833 (0.807, 0.859)		0.07% (−0.22%, 0.36%)	
Budapest	0.857 (0.836, 0.880)		−0.15% (−0.42%, 0.12%)	
Harrow	0.830 (0.768, 0.897)		0.34% (−0.37%, 1.05%)	
Heidelberg	0.867 (0.831, 0.904)		−0.10% (−0.61%, 0.42%)	
Cambridge	0.781 (0.751, 0.812)		0.36% (−0.06%, 0.78%)	
Leuven	0.794 (0.763, 0.827)	−0.25% (−0.34%, −0.16%)	0.39% (−0.09%, 0.87%)	0.51% (0.43%, 0.58%)
Malmö	0.788 (0.738, 0.842)		0.42% (−0.11%, 0.96%)	
Manchester	0.793 (0.740, 0.850)		0.83% (0.16%, 1.52%)	
Moscow	0.839 (0.802, 0.878)		0.02% (−0.56%, 0.60%)	
Oslo	0.793 (0.717, 0.877)		−0.05% (−0.72%, 0.63%)	
Ovidedo	0.848 (0.829, 0.867)		−0.32% (−0.67%, 0.04%)	
Piestany	0.895 (0.834, 0.960)		−0.51% (−1.28%, 0.27%)	
Rotterdam	0.842 (0.815, 0.870)		−0.43% (−0.71%, −0.15%)	

Table C1. Standard deviation of spinal bone density: women

Centre	Intercept	Age
Aberdeen	0.1674 (0.1535, 0.1825)	
Berlin	0.2135 (0.1920, 0.2375)	
Budapest	0.1450 (0.1312, 0.1603)	
Erfurt	0.1972 (0.1739, 0.2235)	
Graz	0.2094 (0.1917, 0.2286)	
Harrow	0.1896 (0.1500, 0.2396)	
Heidelberg	0.2074 (0.1784, 0.2410)	
Cambridge	0.1948 (0.1789, 0.2120)	
Leuven	0.1752 (0.1583, 0.1938)	1.18% (0.84%, 1.52%)
Malmö	0.1479 (0.1279, 0.1711)	
Manchester	0.1771 (0.1452, 0.2160)	
Moscow	0.1889 (0.1655, 0.2155)	
Oslo	0.1685 (0.1509, 0.1882)	
Oviedo	0.1931 (0.1770, 0.2107)	
Piestany	0.1328 (0.1141, 0.1547)	
Rotterdam	0.1783 (0.1629, 0.1952)	

Table C2. Standard deviation of trochanteric bone density: women

Centre	Intercept	Age	Weight
Aberdeen	0.1451 (0.1329, 0.1584)		
Berlin	0.1528 (0.1374, 0.1698)		
Budapest	0.1418 (0.1282, 0.1568)		
Harrow	0.1639 (0.1301, 0.2066)		
Heidelberg	0.1903 (0.1637, 0.2212)		
Cambridge	0.1592 (0.1462, 0.1733)		
Leuven	0.1739 (0.1571, 0.1925)	0.55% (0.17%, 0.93%)	−0.44% (−0.70%, −0.17%)
Malmö	0.1673 (0.1447, 0.1934)		
Manchester	0.1329 (0.1091, 0.1619)		
Moscow	0.1665 (0.1459, 0.1902)		
Oslo	0.1728 (0.1429, 0.2091)		
Oviedo	0.1445 (0.1324, 0.1577)		
Piestany	0.1361 (0.1167, 0.1589)		
Rotterdam	0.1585 (0.1448, 0.1736)		

Table C3. Standard deviation of femoral neck bone density: women

Centre	Intercept	Weight
Aberdeen	0.1365 (0.1250, 0.1490)	
Berlin	0.1582 (0.1425, 0.1757)	
Budapest	0.1167 (0.1056, 0.1288)	
Harrow	0.1423 (0.1129, 0.1793)	
Heidelberg	0.1544 (0.1329, 0.1795)	
Cambridge	0.1495 (0.1373, 0.1627)	
Leuven	0.1556 (0.1407, 0.1722)	−0.38% (−0.65%, −0.12%)
Malmö	0.1545 (0.1338, 0.1784)	
Manchester	0.0892 (0.0733, 0.1086)	
Moscow	0.1627 (0.1425, 0.1858)	
Oslo	0.1416 (0.1171, 0.1713)	
Oviedo	0.1463 (0.1341, 0.1596)	
Piestany	0.1248 (0.1069, 0.1458)	
Rotterdam	0.1470 (0.1344, 0.1608)	

Table C4. Standard deviation of spinal bone density: men

Centre	Intercept	Age
Aberdeen	0.1636 (0.1501, 0.1783)	
Berlin	0.1732 (0.1567, 0.1914)	
Budapest	0.1555 (0.1395, 0.1734)	
Erfurt	0.1554 (0.1349, 0.1790)	
Graz	0.2055 (0.1887, 0.2237)	
Harrow	0.1984 (0.1569, 0.2507)	
Heidelberg	0.2117 (0.1851, 0.2422)	
Cambridge	0.2021 (0.1806, 0.2262)	
Leuven	0.1754 (0.1554, 0.1980)	0.77% (0.41%, 1.14%)
Malmö	0.1654 (0.1418, 0.1931)	
Manchester	0.1516 (0.1142, 0.2013)	
Moscow	0.1777 (0.1509, 0.2093)	
Oslo	0.1707 (0.1522, 0.1915)	
Oviedo	0.1928 (0.1759, 0.2113)	
Piestany	0.1423 (0.1072, 0.1888)	
Rotterdam	0.1716 (0.1567, 0.1879)	

Table C5. Standard deviation of trochanteric bone density: men

Centre	Intercept	Age
Aberdeen	0.1339 (0.1229, 0.1460)	
Berlin	0.1568 (0.1417, 0.1734)	
Budapest	0.1250 (0.1121, 0.1393)	
Harrow	0.1571 (0.1243, 0.1986)	
Heidelberg	0.1627 (0.1419, 0.1865)	
Cambridge	0.1753 (0.1563, 0.1965)	
Leuven	0.1776 (0.1570, 0.2010)	0.48% (0.07%, 0.89%)
Malmö	0.1696 (0.1455, 0.1976)	
Manchester	0.1342 (0.1011, 0.1782)	
Moscow	0.1553 (0.1319, 0.1829)	
Oslo	0.1678 (0.1336, 0.2108)	
Oviedo	0.1681 (0.1533, 0.1842)	
Piestany	0.1157 (0.0872, 0.1535)	
Rotterdam	0.1608 (0.1468, 0.1761)	

Table C6. Standard deviation of femoral neck bone density: men

Centre	Intercept	Age
Aberdeen	0.1416 (0.1299, 0.1544)	
Berlin	0.1413 (0.1277, 0.1563)	
Budapest	0.1166 (0.1046, 0.1301)	
Harrow	0.1675 (0.1325, 0.2117)	
Heidelberg	0.1782 (0.1555, 0.2041)	
Cambridge	0.1628 (0.1452, 0.1825)	
Leuven	0.1686 (0.1490, 0.1908)	0.57% (0.17%, 0.98%)
Malmö	0.1438 (0.1234, 0.1676)	
Manchester	0.1292 (0.0973, 0.1715)	
Moscow	0.1453 (0.1234, 0.1711)	
Oslo	0.1298 (0.1033, 0.1630)	
Oviedo	0.1710 (0.1560, 0.1874)	
Piestany	0.1067 (0.0804, 0.1416)	
Rotterdam	0.1430 (0.1306, 0.1566)	