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ORIGINAL ARTICLE

International variation in proximal femur bone mineral density

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Abstract
Summary We observed higher proximal femur bone mineral density (BMD) in European women compared to average values derived from US Caucasian women in the National Health and Nutrition Examination Survey (NHANES) study. Across European centres, Parisian women had lower proximal femur BMD compared to women from Kiel or Sheffield.
Introduction Proximal femur BMD of US adults (NHANES III) may not accurately reflect that of European women. We examined the heterogeneity of BMD across European and US Caucasian women and across different European populations.
Methods Proximal femur BMD was measured in women ages 20–39 years (n=258) and 55–79 years (n=1,426) from three European centres. Cross-calibrated BMD for total hip, femoral neck, trochanter and intertrochanter were examined. International variation in BMD was assessed by comparing means and SDs in the European data with those from the US NHANES III study. European populations were stratified into 5-year age bands to establish individual centre reference intervals. Between-centre differences were assessed using ANOVA and post hoc Fisher's least significant difference tests.
Results European women had higher BMD than US women: The differences were 7.1% to 14.2% (p<0.001) and 0% to 3.9% (p<0.05) in the older and younger women, respectively. Standard deviations for BMD at the different sites were comparable to those for US women. Among older, but not younger European women, proximal femur BMD was significantly lower in French women (Paris) than in women from Germany (Kiel) or the UK (Sheffield) (difference=5.0% to 9.6%, p<0.05).
Conclusions International variation in hip BMD does exist, with international and between-centre differences being less evident at the femoral neck.

Keywords European · Geographical variation · International comparison · NHANES III · Proximal femur bone mineral density · Reference intervals

The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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Introduction

Reference interval data for proximal femur bone mineral density (BMD) determined using dual-energy X-ray absorptiometry (DXA) have been established in US adults as part of phases I and II of the third National Health and Nutrition Examination Survey (NHANES III) [1, 2]. The use of these data is advocated by the International Society

for Clinical Densitometry (ISCD; www.iscd.org) in the 2007 Official Positions Statement [3], to standardize the clinical interpretation of BMD results obtained using different brands and types of densitometer.

Geographical variation in proximal femur BMD [2, 4–7], however, has been shown to exist. European differences in proximal femur BMD have been demonstrated within pre- and post-menopausal populations in the Network in Europe on Male Osteoporosis (NEMO) study [4] and the European Vertebral Osteoporosis Study (EVOS) [5]. In addition, regional within-country variation in proximal femur BMD has been observed [2, 6]. The variation in proximal femur BMD data between European populations appears greater than that seen between US regions [6].

Bone mineral density measurements in the aforementioned studies were predominantly performed using pencil-beam technology and a variety of densitometers manufactured by different companies. There are currently no population-based reference intervals for proximal femur BMD based on a single type and brand of fan-beam densitometer. Some studies have reported between-country differences in femoral neck and trochanteric BMD, but there is little information available about the European and international heterogeneity of BMD data acquired in other regions of interest, including the total hip and intertrochanter.

We hypothesized that NHANES III proximal femur reference intervals may not accurately reflect average BMD values in European women and wished to identify international variation in BMD at all sites of the proximal femur.

The aims of this study were to (1) establish normal reference intervals for proximal femur BMD in European women, (2) examine the variation in proximal femur BMD between (a) European and US Caucasian women and (b) different European countries and (3) extend current knowledge of the international variation in BMD measured by fan-beam technology at different regions of interest in the proximal femur.

Materials and methods

Study design

The Osteoporosis and Ultrasound (OPUS) study, previously described by Glueer et al [8], is a multi-centre population-based study involving four European countries. Five centres including Aberdeen (Department of Medicine and Therapeutics, University of Aberdeen, Aberdeen, UK), Berlin (Diagnostische Radiologie, Klinikums, Benjamin Franklin der Freien Universität Berlin, Berlin, Germany), Kiel (Medizinische Physik, Klinik für Diagnostische Radiologie, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Kiel, Germany), Paris (Paris Descartes University, Cochin Hospital, Department of Rheumatology, Paris, France) and Sheffield (Academic Unit of Bone Metabolism, University of Sheffield, Northern General Hospital, Sheffield, UK) participated in the study.

Caucasian women who participated in the baseline visit of the OPUS study were included in this analysis. The population comprised younger women, ages 20 to 39 years (n=258), and older women, ages 55 to 79 years (n=1426). The women had been recruited from random population samples in Sheffield (UK), Kiel (Germany) and Paris (France), between April 1999 and April 2001. In Sheffield, women registered on general practice lists and meeting the study inclusion criteria were targeted using letters of invitation. In Kiel, women were randomly selected from government-provided registers ('Einwohnermeldeamtslisten') and were initially contacted by mail. A similar procedure was followed in France, using registers of a complementary health insurance system. Recruitment was monitored and adjusted accordingly throughout the study period, to attempt to achieve a homogeneous distribution across the age range. Exclusion criteria were limited to disorders that precluded valid study measurements (e.g. bilateral hip prostheses), general inability to undergo specific examinations and cognitive limitations that would prevent the completion of self-administered questionnaires and pregnancy (to avoid exposure of a foetus to ionizing radiation).

The OPUS study was registered with and approved by Local Research Ethics Committees in the UK, Germany and France, and all women gave their written informed consent prior to participation in the study. All investigations were carried out in accordance with the good clinical practice guidelines established during the International Conference on Harmonization and the Declaration of Helsinki (ICH GCP).

Densitometry

Bone mineral density of the proximal femur was measured by DXA in the posteroanterior projection. The measurements in Sheffield, Kiel and Paris were performed using Hologic QDR 4500 Acclaim densitometers (Hologic Inc., Bedford, MA, USA). Two further study centres, Berlin (Germany) and Aberdeen (UK), participated in the OPUS study, but the BMD data were collected using GE/Lunar densitometers and thus are not included in the current analyses. Four regions of interest, namely the total hip, femoral neck, trochanter and intertrochanter, were studied.

Daily measurements of the local anthropomorphic phantom and European Spine Phantom (ESP) were performed at each centre, and the stability of the densitometry equipment was monitored. A 'travelling' ESP was measured ten times at each study centre in order to cross-calibrate the data produced

by the three densitometers [9]. Proximal femur BMD was cross-calibrated to the mean BMD of vertebrae L2 to L4 of the 'travelling' ESP phantom in accordance with the method described by Genant et al. [10]. Cross-calibrated BMD data were calculated for total hip (xTHBMD), femoral neck (xFNBMD), trochanter (xTBMD) and intertrochanter (xITBMD).

All densitometry measurement standard operating procedures were devised by the OPUS study coordinating centre (Kiel) and standardized in accordance with manufacturer-specified guidelines. The study was directed by the OPUS study Steering Committee [8].

Data and statistical analyses

The OPUS study population was stratified into 10-year age bands to establish an overall European reference interval for proximal femur BMD, acquired using Hologic densitometers, of the total hip, femoral neck, trochanter and intertrochanter. International variation in BMD in all regions of the proximal femur was then assessed using hypothesis testing; the null hypothesis was that, on average, BMD in European and US Caucasian women does not differ significantly. Bone density at the Ward's triangle was not evaluated during these analyses as the clinical use of these data is not advocated by the ISCD.

The European reference intervals for proximal femur BMD, of the total hip, femoral neck, trochanter and intertrochanter at the individual centres were established by stratifying the study populations from Sheffield, Kiel and Paris into 5-year age bands. ANOVA and Fisher's least significant difference post hoc tests were used to examine variations in the anthropometric characteristics and the proximal femur BMD of the women from the three OPUS study centres. The influence of anthropometric characteristics on between-centre differences in proximal femur BMD was studied using multi-factorial analysis of variance with BMD as the dependant variable and age and centre as factors (independent variables). The covariates were defined as weight, height and BMI. A type III sum of squares approach was adopted to determine the independent influence of each factor and covariate on BMD.

Data were analyzed using Statgraphics Plus V5.0 (Statistical Graphics Corp., Manguistics, Inc., Cambridge, MA, USA). A level of $p<0.05$ was selected to indicate statistical significance.

Results

Proximal femur BMD in older European women (age bands 60 to 69 and 70 to 79 years) was significantly higher at all regions of interest (absolute difference=0.048 to 0.085 g/cm^2, percent difference=7.1% to 14.2%, $p<0.0001$ to $p=0.018$) compared to that for US women (Fig. 1). Higher mean values were also observed in the younger European women for xITBMD in the age band 20 to 29 years (absolute difference=0.040 g/cm^2, percent difference=3.6%, $p=0.011$) and for xTHBMD and xTBMD in the age band 30 to 39 years (absolute difference=0.027 to 0.035 g/cm^2, percent difference=3.8% and 3.9%, $p=0.01$ to $p=0.02$). Differences in xFNBMD between European and US women were less evident (Fig. 1).

The characteristics of the European OPUS study population, stratified into 5-year age bands, are shown in Table 1. Between-centre differences in the anthropometric characteristics of the OPUS population were observed. Women from Kiel were taller (all age bands except 25 to 29 years, absolute difference=3.2 to 9.8 cm, percent difference=2.0% to 6.0%, $p=0.0066$ to $p<0.0001$) than those from Sheffield or Paris. Women from Sheffield were heavier (all age bands for the older women and the 25 to 29 years age band, absolute difference=6.1 to 14.6 kg, percent difference=10.1% to 27.3%, $p=0.0039$ to $p<0.0001$) and had a higher BMI (all age bands for the older women and the 25- to 29-year age band, absolute difference=2.1 to 4.4 kg/m^2, percent difference=8.5% to 21.9%, $p=0.0045$ to $p<0.0001$). Older women from Paris had lower xTHBMD, xTBMD and xITBMD (all age bands except 75 to 79 years, absolute difference=0.050 to 0.058 g/cm^2, percent difference=6.0% to 9.6%, $p<0.0001$ to $p=0.029$), xFNBMD (age band=60 to 64 years, absolute difference=0.052 g/cm^2, percent difference=7.2%, $p=0.002$) than Sheffield and Kiel. Inter-centre differences in xFNBMD were less well defined. The proximal femur BMD of younger women did not differ significantly between the centres, but there was a tendency for Sheffield women, in the 20- to 39-year age bands, to have higher proximal femur BMD than those from Kiel or Paris (Fig. 2 and Table 2).

Anthropometric factors in the European women were associated with BMD at the trochanteric site only, where it was higher in heavier ($p=0.036$) and taller ($p=0.036$) individuals. Body mass index was not independently associated with proximal femur BMD.

Discussion

The OPUS study is a large population-based, multi-centre study that provides information about proximal femur BMD, acquired using a single brand and type of densitometer and fan-beam technology. We have established normal reference intervals for younger and older European women and contributed to current knowledge about the international and European variation in proximal femur BMD. To date, this is

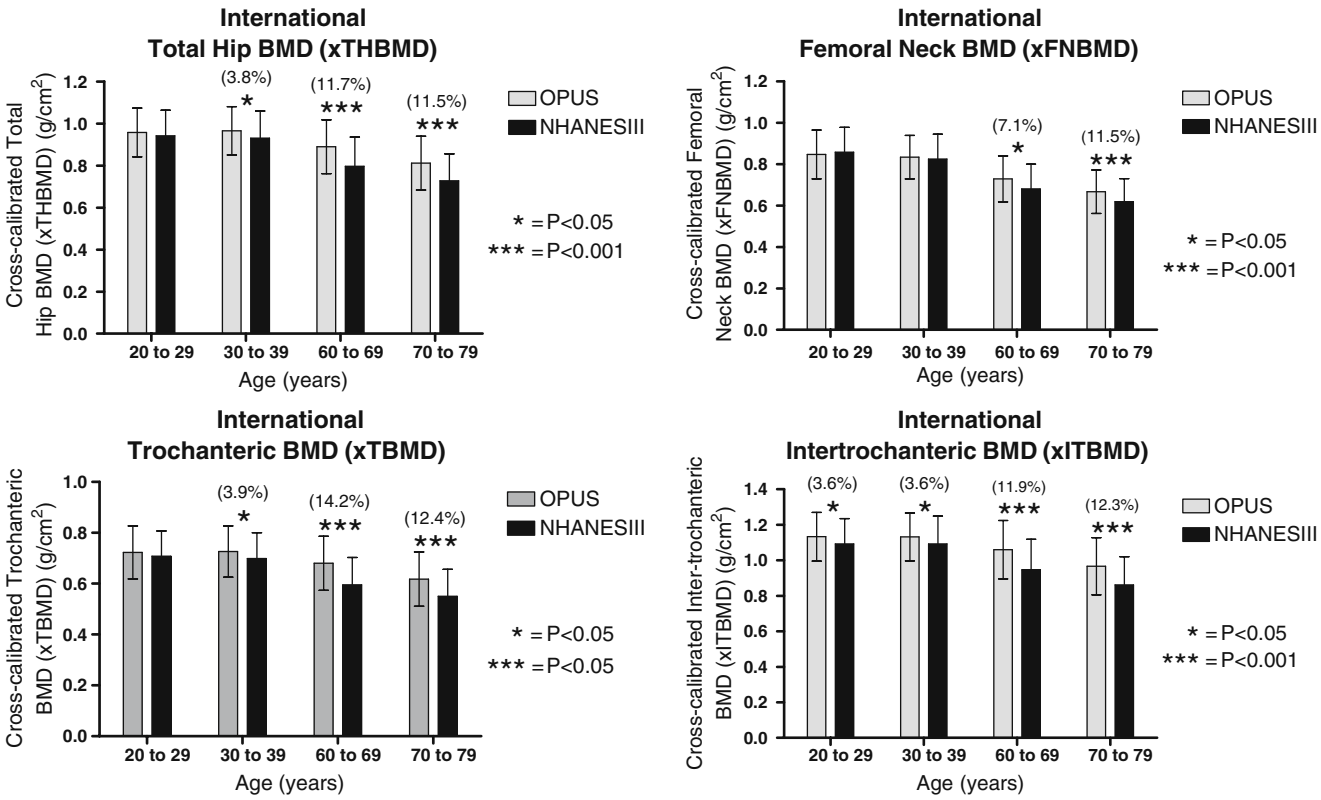

Fig. 1 Cross-calibrated proximal femur BMD (mean ± SEM) in Caucasian women from the OPUS (Europe) and NHANES III (USA) studies, stratified by 10-year age bands. Results are presented as total hip bone mineral density (*xTHBMD*; *top left*), femoral neck bone mineral density (*xFNBMD*; *top right*), trochanteric bone mineral density (*xTBMD*; *bottom left*) and intertrochanteric bone mineral density (*xITBMD*; *bottom right*). The percent differences between the NHANES III and OPUS are indicated in *parenthesis*

the only study where European and US BMD data for all regions of interest at the proximal femur have been compared in Caucasian women over an age range of 20 to 79 years. Published reports of international comparisons of proximal femur BMD are few; hence, the results of our study contribute substantially to this area of knowledge.

We observed that reference intervals from NHANES III were significantly lower than those obtained in the OPUS study; this indicates that significant differences in proximal femur BMD exist between US and European Caucasian women. The results of an international comparison of trochanteric and femoral neck BMD were discussed by Kaptoge et al. [4] following the evaluation of the NEMO study data collected in young European men and women, but BMD data at other proximal femur sites were not presented. Kaptoge et al. found that young European women had lower mean BMD ($p<0.0001$ for both trochanteric and femoral neck regions) than their US counterparts, but the standard deviations for the NEMO and NHANES III populations were similar [2, 4]. We found that the standard deviations of proximal femur BMD in OPUS study participants were comparable to those reported by Looker et al. for US women [2].

A visual examination of the anthropometric data collected during the NHANES III study revealed some differences in the characteristics of US and European women [11]. Younger US women (30 to 39 years) were found to be heavier and had higher BMIs than young European women, whereas young European women (20 to 29 years) were taller. Differences in the weight and BMI of the older women were evident in the 50- to 59-year age band only with US women being heavier and having a higher BMI. Noon et al. [12] reported a highly statistically significant relationship between Z-score and weight at each BMD site during a multi-centre UK study; heavier and taller OPUS participants were found to have higher BMD at the trochanteric site only. The centre-specific weight data collected during the OPUS study, however, do not seem to explain the observed European centre-specific differences in BMD.

We demonstrated considerable heterogeneity in the proximal femur BMD of both younger and older Caucasian women from different European countries. Similar results have been published from the EVOS and NEMO studies [4, 5], predominantly for data obtained using pencil-beam densitometers; Lunt et al. and Kaptoge et al. reported differences in femoral neck and trochanteric BMD in both

Table 1 Characteristics of the OPUS population for younger (n=258, 20 to 39 years) and older women (n=1,426, 55 to 79 years), shown as age-specific (5-year age bands) mean ± standard deviation

Age band (years)	Number	Age (years)	Height (cm)	Weight (kg)	BMI (kg/cm^2)
OPUS					
20 to 24	33	23.1±1.0	166±6*	70.5±15.0	25.5±5.4
25 to 29	71	27.6±1.3	167±7	63.9±11.3*	22.9±3.5*
30 to 34	72	32.6±1.4	167±7**	64.3±9.7	23.2±3.3
35 to 39	82	37.7±1.4	165±6**	65.6±10.9	24.1±3.9
55 to 59	324	57.5±1.3	162±6**	68.6±12.9**	26.1±4.8**
60 to 64	315	62.6±1.3	161±6**	70.2±13.3**	27.0±5.0**
65 to 69	288	67.4±1.4	161±6**	68.7±12.2**	26.6±4.4**
70 to 74	273	72.4±1.4	159±6**	66.7±12.1**	26.3±4.5**
75 to 79	226	77.4±1.4*	158±6**	65.3±10.4*	26.0±3.7*
Sheffield					
20 to 24	18	23.3±1.1	164±5	73.9±18.0	27.5±6.1
25 to 29	29	27.9±1.3	167±7	68.1±14.0	24.5±4.6
30 to 34	22	32.5±1.5	162±5	63.6±7.8	24.1±2.7
35 to 39	24	37.8±1.4	163±7	68.0±9.6	25.5±3.3
55 to 59	100	57.4±1.3	161±5	72.4±15.0	27.9±5.3
60 to 64	95	62.6±1.4	160±6	74.8±14.3	29.0±5.1
65 to 69	98	67.3±1.5	159±5	71.4±12.3	28.1±4.4
70 to 74	92	72.3±1.5	158±6	68.4±11.1	27.2±4.3
75 to 79	96	77.3±1.5	157±6	66.5±10.2	26.8±3.5
Kiel					
20 to 24	13	22.8±0.9	166±4	66.2±8.9	23.3±3.1
25 to 29	35	27.3±1.4	168±7	62.4±7.4	22.0±2.0
30 to 34	32	32.8±1.2	170±6	64.5±8.5	22.4±2.9
35 to 39	25	37.4±1.5	169±5	67.0±9.2	23.3±3.0
55 to 59	102	57.7±1.2	164±6	70.2±11.1	26.1±4.3
60 to 64	124	62.5±1.2	164±6	71.4±12.2	26.6±4.6
65 to 69	106	67.6±1.2	163±6	70.9±10.9	26.6±3.9
70 to 74	98	72.7±1.3	162±6	70.4±12.2	27.0±4.6
75 to 79	82	77.8±1.2	160±5.4	66.7±9.7	25.9±3.6
Paris					
20 to 24	2	22.4±0.4	174±4	69.0±17.0	22.8±4.7
25 to 29	7	27.9±0.7	163±10	53.6±6.2	20.1±1.0
30 to 34	18	32.4±1.6	166±8	65.0±13.7	23.5±4.3
35 to 39	33	38.0±1.3	163±5	63.0±12.5	23.7±4.7
55 to 59	122	57.5±1.4	166±6	64.2±11.3	24.7±4.3
60 to 64	96	62.6±1.4	159±6	64.1±11.5	25.3±4.7
65 to 69	84	67.3±1.4	159±6	62.9±11.7	25.0±4.4
70 to 74	83	72.2±1.5	157±6	60.6±10.5	24.6±4.1
75 to 79	48	77.1±1.5	156±6	60.6±10.9	24.7±3.9

*p<0.01; **p<0.001 indicate significant between-centre differences in the characteristics of the OPUS population (comprising of women from Sheffield, Kiel and Paris)

older and younger European women. Kaptoge et al. reported that 74% and 91% of the observed variation in femoral neck and trochanteric BMD, respectively, could be attributed to true between-centre differences [4]. We did not observe any significant between-centre differences in the younger women however, and this may have been due to the smaller numbers of women recruited into the 20- and 30-year age bands.

International and between-centre differences in BMD were less evident for the femoral neck region. In light of this finding, it could be assumed that the femoral neck is the preferred site for measurement and interpretation of proximal femur BMD. The ISCD [3] advocate the use of the lowest of either the femoral neck BMD or total proximal femur BMD as a means by which a diagnosis of osteoporosis can be made. The clinical use of total proximal femur BMD has an

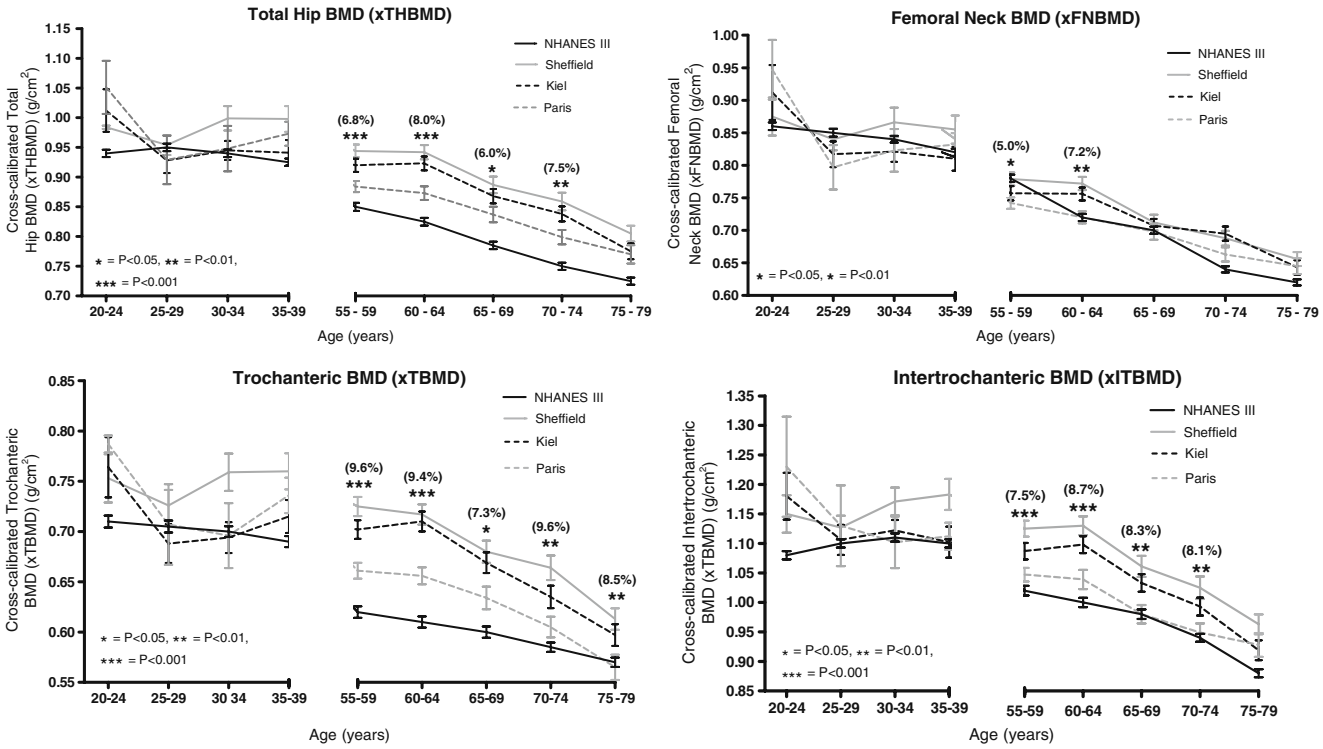

Fig. 2 Cross-calibrated proximal femur BMD (mean ± SEM) in Caucasian women from three centres participating in the OPUS study (Europe), stratified by 5-year age bands, together with NHANES III reference interval data. Results are presented as total hip bone mineral density (*xTHBMD*; *top left*), femoral neck bone mineral density (*xFNBMD*; *top right*), trochanteric bone mineral density (*xTBMD*; *bottom left*) and intertrochanteric bone mineral density (*xITBMD*; *bottom right*). *$p<0.05$, **$p<0.01$ and ***$p<0.001$ indicate significant between-centre difference for the OPUS study. The percent differences between the highest and lowest centres are indicated in *parenthesis*

advantage over femoral neck BMD for patient follow-up, with total proximal femur BMD measurements having better precision due to the larger area being scanned.

All DXA measurements used in our analysis were performed using the same brand and type of densitometer; however, slight inherent performance differences are known to exist between devices. Well-established cross-calibration procedures were adopted during our study [9, 10], but highly significant differences in proximal femur BMD were still evident between different European study centres. Similarly, in the NEMO study, there was significant between-centre heterogeneity in both women and men even after adjustment for age, height and weight [4]. These differences remained even after cross-calibration and standardization of BMD data collected during the EVOS study and following correction for anthropometric factors [5]. We used the established method of cross-calibrating densitometers using the ESP as described by Genant et al. [10]. The anthropomorphic design of the ESP offers an excellent overall means of acquiring cross-calibrated BMD data within the 'typical' clinical range; however, it cannot truly mimic the anatomical and physiological variation within the human spine, and there are also obvious anatomical differences between the spine and the proximal femur. Alternative methods based on the use of 'biological calibrants', however, are not feasible.

An international meta-analysis of proximal femur BMD data in men and women (n=39,000) from North America, Europe, Australia and Asia concluded that low proximal femur BMD is a significant indicator of hip fracture risk [13]. Older Parisian women participating in the OPUS study had significantly lower proximal femur BMD than women of a similar age from Sheffield or Kiel. This could suggest that Parisian women are at higher risk of hip fracture. Our study has also shown that US women participating in the NHANES III study have lower proximal femur BMD than those from the OPUS study population, and thus, US women may be at higher risk of sustaining hip fracture than their European counterparts. It is likely that the extent of the relationship between proximal femur BMD and hip fracture risk varies from country to country.

Numerous other factors including, for example, geographic, genetic, environmental, lifestyle, dietary and other factors have been investigated as potential determinants of BMD [7, 14–16]. These factors also influence the variation in proximal femur BMD, hip fracture risk and the incidence rate for hip fracture that is evident between countries or continents [17–19]. Although proximal femur BMD is an

Table 2 Cross-calibrated bone mineral density (mean ± SD) for younger (20 to 39 years) and older women (55 to 79 years) shown as age-specific (5-year age bands) mean and standard deviations

Age band (years)	Number	Total hip BMD (xTHBMD; g/cm^2)	Femoral neck BMD (xFNBMD; g/cm^2)	Trochanteric BMD (xTBMD; g/cm^2)	Intertrochanteric BMD (xITBMD; g/cm^2)
OPUS[a]					
20 to 24	33	0.999±0.120	0.894±0.132	0.760±0.100	1.167±0.135
25 to 29	71	0.938±0.110	0.824±0.104	0.706±0.102	1.117±0.136
30 to 34	72	0.962±0.114	0.835±0.108	0.715±0.105	1.132±0.131
35 to 39	82	0.970±0.115	0.832±0.103	0.737±0.096	1.132±0.139
55 to 59	324	0.914±0.110	0.759±0.103	0.694±0.095	1.084±0.137
60 to 64	315	0.913±0.122	0.751±0.103	0.696±0.102	1.099±0.162
65 to 69	288	0.865±0.129	0.706±0.114	0.662±0.108	1.027±0.161
70 to 74	273	0.833±0.128	0.683±0.106	0.636±0.110	0.990±0.162
75 to 79	226	0.787±0.123	0.649±0.099	0.567±0.100	0.939±0.156
Sheffield					
20 to 24	18	0.984±0.119	0.875±0.124	0.753±0.102	1.150±0.135
25 to 29	29	0.954±0.090	0.830±0.090	0.726±0.083	1.127±0.108
30 to 34	22	0.997±0.096	0.866±0.104	0.759±0.087	1.171±0.111
35 to 39	24	0.998±0.106	0.844±0.105	0.760±0.088	1.183±0.129
55 to 59	100	0.944±0.109	0.769±0.100	0.725±0.095	1.125±0.135
60 to 64	95	0.942±0.116	0.772±0.099	0.717±0.098	1.130±0.156
65 to 69	98	0.887±0.138	0.712±0.118	0.680±0.110	1.061±0.176
70 to 74	92	0.860±0.143	0.688±0.110	0.664±0.117	1.052±0.185
75 to 79	96	0.805±0.131	0.656±0.105	0.613±0.104	0.963±0.165
Kiel					
20 to 24	13	1.012±0.129	0.912±0.151	0.764±0.108	1.180±0.143
25 to 29	35	0.927 ±0.125	0.817±0.117	0.688±0.114	1.106±0.150
30 to 34	32	0.945±0.091	0.829±0.089	0.694±0.087	1.123±0.101
35 to 39	25	0.940±0.120	0.810±0.103	0.715±0.096	1.102±0.149
55 to 59	102	0.920±0.112	0.758±0.111	0.702±0.093	1.087±0.140
60 to 64	124	0.923±0.129	0.756±0.111	0.710±0.110	1.098±0.160
65 to 69	106	0.868±0.124	0.707±0.110	0.669±0.106	1.033±0.523
70 to 74	98	0.838±0.124	0.695±0.108	0.637±0.111	0.993±0.151
75 to 79	82	0.775±0.120	0.643±0.100	0.597±0.098	0.919±0.153
Paris					
20 to 24	2	1.051±0.062	0.787±0.012	0.947±0.064	1.230±0.120
25 to 29	7	0.929±0.108	0.797±0.090	0.707±0.106	1.130±0.181
30 to 34	18	0.948±0.162	0.823±0.139	0.696±0.138	1.102±0.186
35 to 39	33	0.973±0.116	0.832±0.101	0.736±0.100	1.118±0.132
55 to 59	122	0.884±0.103	0.742±0.100	0.661±0.087	1.047±0.127
60 to 64	96	0.873±0.112	0.720±0.091	0.656±0.083	1.039±0.160
65 to 69	84	0.837±0.120	0.700±0.114	0.634±0.011	0.980±0.020
70 to 74	83	0.800±0.109	0.663±0.100	0.605±0.094	0.949±0.140
75 to 79	48	0.770±0.107	0.645±0.084	0.565±0.870	0.928±0.140

[a] The OPUS population comprised of women from Sheffield, Kiel and Paris

important factor in the determination of hip fracture risk, these other influences must be also considered. However, an in-depth analysis of such influences is beyond the scope of this report.

Our study has some limitations. We studied women over a wide age range, but BMD data were obtained from three centres only; thus, the study population may not fully represent all European women.

Different recruitment methods, including the use of general practice registers and government-provided registers, were applied at the three centres. Although all the participants were randomly recruited, there may have been some population selection bias. We aimed to recruit equal numbers of subjects in each age band; however, some age bands may not have been adequately represented. The recruitment of younger women, particularly the 20- to 24-year age band, was problematic for all three centres. Fewer younger women in the 25- to 29-year age band were recruited by the centre in Paris when compared to Sheffield and Kiel. As many of the women in the younger age bands worked and/or had young families, the recruitment of these subjects was extremely challenging. This may have influenced the accuracy of the estimates of young normal BMD at the proximal femur or the between-centre differences in BMD. Overestimation of the SDs for BMD may have resulted from the small number of women in age bands 20 to 24 and 25 to 29 years. Small recruitment numbers, however, do not always result in larger SDs. Consequently, it is difficult to draw conclusions for the women in these age bands.

Only those individuals who were physically capable of travelling to the study centres were able to participate in the OPUS study, and this may have excluded a large proportion of the elderly population including those with severely impaired mobility, the house-bound and those living in residential care. These women are more likely to have lower proximal femur BMD and are consequently at a higher risk of sustaining a hip fracture. Women >70 years of age may have been under represented in this study, and thus, proximal femur BMD in the general population may be somewhat lower.

In conclusion, there is significant European and international variation in proximal femur BMD which may lead to differences in fracture risk. This needs to be taken into account in the clinical interpretation of BMD results for patients originating from different geographic locations. No single approach has been advocated, but the use of local BMD reference ranges and country-specific adjustment factors resulting in the regional correction of T- and Z-scores have been suggested. Both approaches, however, are problematic and may be difficult to apply, leading to inconsistent BMD estimates and inaccurate interpretation of these data. Currently, the interpretation of BMD data for diagnostic purposes should only be made as part of a comprehensive risk assessment including a risk factor questionnaire, which may reveal specific geographical risk factors, e.g. limited sunlight exposure, and if clinically indicated further investigation of underlying causes. The centre-specific data presented for BMD should be interpreted with caution, particularly for young Parisian women. Therefore, until further knowledge about regional and international variation in proximal femur BMD has been gained, NHANES III should remain the preferred reference interval data source.

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Conflicts of interest None.

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