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Adjustment of DXA BMD Measurements for Anthropometric Factors and its Impact on the Diagnosis of Osteoporosis

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Declarations

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Conflicts of interest: Ling Wang, Limei Ran, Xiaojuan Zha, Kaiping Zhao, Yingying Yang, Qing Shuang, Yandong Liu, Karen Hind, Xiaoguang Cheng, Glen M Blake declare that they have no conflicts of interest.

Ethics approval: The study was approved by the ethics committee of Beijing Jishuitan hospital.

Consent to participate: Each participant in the study gave written informed consent for their data to be used.

Consent for publication: All authors agree to the publication of this article.

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Mini Abstract

We compared the effect of anthropometric factors on osteoporosis diagnosis by QCT and DXA and found QCT spine vBMD was not associated with body weight, BMI or DXA anteroposterior spine thickness. In contrast, DXA spine and hip aBMD were strongly associated with all three factors. Adjustment of DXA aBMD measurements improved consistency with QCT vBMD.

Abstract

Purpose Although the diagnosis of osteoporosis using DXA T-scores preferentially targets patients with lower body mass index (BMI), there is evidence that obesity is not protective against fractures. The aim of this study was to compare the effect of anthropometric factors on osteoporosis diagnosis by QCT and DXA and investigate whether adjustment of DXA aBMD can achieve a more even distribution of diagnoses between slimmer and heavier individuals consistent with QCT.

Methods The participants were 964 men and 682 women referred for low dose chest CT and DXA examinations as part of their employers' health check-up programs. QCT vBMD was measured in the L1-L2 vertebrae and DXA aBMD in the spine and hip. The prevalence of osteoporosis in each tertile of BMI in participants aged >50 years was evaluated based on their QCT and DXA findings, and then re-evaluated after adjustment to the mean BMI in each sex. Similar investigations were performed for body weight and DXA anteroposterior (AP) spine thickness. The effect of the adjustment of DXA aBMD for anthropometric factors on the correlation with QCT vBMD was also examined.

Results For spine QCT correlations of age adjusted vBMD residuals against BMI were not statistically significant in men ($P=0.44$) or women ($P=0.32$). In contrast, slopes for aBMD residuals were all highly statistically significant ($P<0.001$). There were similar findings for weight and AP spine thickness. Adjustment of DXA aBMD for anthropometric factors resulted in a more equal spread of diagnoses of osteoporosis and greater consistency with QCT.

Conclusion Our study highlights differences between DXA and QCT in their correlation with anthropometric factors and its effect on the diagnosis of osteoporosis. Adjustment of DXA T-scores for anthropometric factors gave greater consistency with QCT vBMD. **Further**

1 studies are required into whether adjusting DXA aBMD for anthropometric factors has a
2 beneficial impact on the discriminative or predictive power for vertebral fracture.
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5 **Key Words:** DXA; QCT; Body weight; BMI; Spine thickness; Diagnosis; Osteoporosis
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7 **Introduction** 8 9

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11 With the ageing of society, osteoporosis has become a significant health problem around the
12 world [1-3]. Bone mineral density (BMD) plays a central role in the diagnosis of osteoporosis,
13 the estimation of fracture risk and the monitoring of treatment [1,2,4,5]. BMD is the mass of
14 bone mineral per unit volume [the volumetric density (vBMD) in units of mg cm^{-3}] measured
15 by quantitative computed tomography (QCT), or per unit area [the areal density (aBMD) in
16 units of g cm^{-2}] measured by dual energy X-ray absorptiometry (DXA). Although both can be
17 measured in vivo by densitometric techniques, DXA is the most widely used method around
18 the world and is recommended by all osteoporosis guidelines [1,2,6]. Although QCT has the
19 advantage of measuring the true volumetric BMD and separating trabecular bone from
20 cortical bone [7], it features less prominently in guidelines [2,5,8,9]. However, in daily
21 clinical practice CT examinations of the abdomen and thoracic region are more frequently
22 performed than DXA and present a valuable and underutilised opportunity to acquire
23 measurements of hip and spine vBMD [10,11].
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45 Although DXA scans predict fracture risk [12], due to their two-dimensional
46 projection nature, DXA derived aBMD measurements are subject to a number of limitations
47 [4]. Areal aBMD measures the superposition of cortical and trabecular bone and results are
48 dependent on bone size. Carter et al. proposed the use of bone mineral apparent density
49 (BMAD, g cm^{-3}) to compensate for differences in bone size by correcting aBMD for the
50 anteroposterior (AP) spine thickness [13]. Absorptiometric measurements at the spine and hip
51 are also influenced by variations in soft tissue thickness and composition because DXA
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1 manufacturers' algorithms make assumptions about the homogenous disposition of fat in the
2 body that in reality are not true [4]. Studies of the accuracy errors in DXA aBMD
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4 measurements at the spine and hip caused by soft tissue inhomogeneity suggest that these can
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6 be substantial [14-16]. Recent studies suggest that obesity may be a risk factor for vertebral
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8 fracture [17-19]. Liu et al. proposed the use of weight corrected bone mineral content (wBMC)
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10 to reduce the over-diagnosis of osteoporosis in lighter weight patients and its under-diagnosis
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12 in heavier patients [20]. Even with the known dependence of aBMD data on bone size and
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14 body weight, all the national and international osteoporosis guidelines continue to recommend
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16 the use of DXA aBMD measurements without any adjustment for BMI, weight or bone size
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25 The adjustment of vBMD and aBMD measurements for anthropometric factors such
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27 as BMI, weight and AP spine thickness and their impact on the diagnosis of osteoporosis has
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29 not been investigated before using QCT and DXA scans in the same population. Therefore, in
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31 the present study we sought to determine the effect of BMI, weight and bone size on vBMD
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33 by QCT and aBMD by DXA using data from a healthy Chinese population referred for their
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35 annual health check-up. After finding that all three factors were significant predictors of DXA
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37 aBMD, but not for QCT vBMD, we explored the impact of the adjustment of DXA aBMD for
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39 anthropometric factors on the diagnosis of osteoporosis and the correlation between aBMD
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41 and QCT vBMD.
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48 **Material and Methods**

49 **Participants**

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52 The study was approved by the ethics committee of Beijing Jishuitan Hospital and
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54 each participant gave written informed consent for their data to be used. Participants were a
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56 subset of the China Biobank project, a prospective nationwide multi-centre cohort study
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1 registered with the US clinical trials database (clinicaltrials.gov; trial identifier:
2 NCT03699228) [21]. The subjects were >30 years old and were originally referred to the
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4 health management centres of the affiliated hospital of Guiyang Medical University, and the
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6 affiliated Yijishan Hospital of Wannan Medical University, as part of their employers' health
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8 check-up programs, and received a low dose chest CT (LDCT) scan for lung cancer screening
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10 and a DXA examination for the measurement of aBMD with both scans performed on the
11
12 same day. Subjects with metal implants within the CT or DXA scan fields were excluded. A
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14 total of 964 men and 682 women were included in the study, which involved the post-scan
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16 processing of CT and DXA scans. No additional radiation was involved.
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22 **Anthropometry measurements**

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25 Weight (kg) and height (m) were measured using calibrated digital scales and
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27 stadiometers and body mass index was calculated [$BMI = \text{weight (kg)}/\text{height (m)}^2$]. Following
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29 the definition of BMAD by Carter et al., DXA AP spine thickness was defined as the square
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31 root of the average projected area of the L2-4 vertebra [$\sqrt{(L2-4 \text{ area}/3)}$] [13].
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36 **QCT and DXA scans**

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39 The details of the China Biobank study protocol have been published elsewhere [21].
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41 All participants in this study received an annual health check-up as part of their employer's
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43 workplace welfare scheme. LDCT scans were conducted on a Supria CT scanner (Hitachi,
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45 Tokyo, Japan) at the Guiyang centre and an Optima CT540 CT scanner (GE Healthcare, WI,
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47 USA) at the Wannan centre. LDCT is now the standard for lung cancer screening [22] and the
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49 subsequent analysis of these CT scans enabled evaluation of vBMD at L1 and L2 using the
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51 Mindways QCT Pro software calibrated with a QCT phantom (Mindways, Austin, TX, USA)
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53 [21]. The regions of interest were defined as the oval-shaped areas containing the largest area
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2 of trabecular bone in the mid-plane of each vertebral body, not including cortical bone or the
3 basivertebral plexus.
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5 DXA measurements of aBMD and lumbar spine projected area were conducted using
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7 GE Lunar DXA (GE Lunar Prodigy and DPX Bravo DXA scanners, GE Healthcare, WI,
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9 USA) systems, GE Lunar Encore software and GE Lunar positioning devices to enable
10 consistency and accuracy of patient positioning. The lumbar spine (L2-4) scan was performed
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12 at the Wannan Centre, and scans of the lumbar spine (also L2-4) and hip were performed at
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14 the Guiyang Centre. DXA and LDCT were performed on the same day. All data were
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16 transferred to the Data Management Centre (Beijing Jishuitan Hospital) for data cleaning and
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18 analysis.
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25 **Statistical Analysis**

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28 All statistical analyses were performed using Microsoft Excel and the Vassarstats
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30 statistical computation web browser [23]. Where descriptive data were normally distributed
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32 results were described as the mean and standard deviation (SD) and analysed using parametric
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34 statistical tests. Otherwise, data were described by the median and analysed using non-
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36 parametric tests.
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42 BMD measurements at each site were plotted against age and fitted by linear regression.
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44 In men, QCT spine vBMD values declined linearly with age between 30 and 60 years, with a
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46 slower rate of loss in those aged >60 years, and the data were fitted in two segments. For
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48 DXA spine aBMD, a number of the men age >70 years had elevated BMD results attributed
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50 to degenerative disease. Therefore men in this age group were excluded from further analysis
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52 and the data for men <70 years fitted by a single regression line. DXA femoral neck and total
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54 hip BMD were both fitted by a single regression line over all ages. For women the plots of
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56 QCT vBMD and DXA aBMD against age were fitted in three segments: a constant BMD for
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1 women aged <45 years, a linear decrease from age 45 to 60, and a shallower linear decrease
2 in those aged >60. Since QCT and DXA measurements have different units (mg cm^{-3} and g
3 cm^{-2} respectively) the residuals from the linear regression lines were converted into Z-scores
4 by dividing by the young adult population SD (QCT: 25 mg cm^{-3} , spine DXA and femoral
5 neck DXA in women: 0.12 g cm^{-2} , other DXA sites: 0.13 g cm^{-2}). Z-scores for each sex and
6 skeletal site were plotted against age to confirm that the mean Z-score and slope of the
7 regression line were both zero.
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18 Z-scores were also plotted against weight, height, BMI and AP spine thickness. At each
19 DXA site the correlation coefficient was largest for the scatter plot against weight, least for
20 the plot against height and intermediate for BMI and spine thickness (Table 1). Weight, BMI
21 and spine thickness were therefore selected as anthropometric factors for further analysis and
22 the slopes of their regression lines with Z-score and their standard errors (SE) evaluated for
23 men and women for QCT and each DXA site. From this analysis it was unclear whether a
24 linear relationship between Z-score and the anthropometric measurement applied over the
25 entire range. For weight this relationship was examined by dividing subjects into 10 kg
26 intervals (men: 40-49, 50-59, 60-69, 70-79, 80-89 and 90+ kg; women 40-49, 50-59, 60-69,
27 70-79 and 80+ kg) and the mean Z-score and SE for each bin plotted against weight. Chi-
28 squared tests were performed to evaluate the goodness of fit of the points to a straight line.
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46 The prevalence of osteoporosis in men and women aged 50 years and over was
47 evaluated based on their QCT and DXA findings. For QCT, osteoporosis was defined as
48 $\text{vBMD} < 80 \text{ mg cm}^{-3}$. For DXA, T-scores were calculated using the GE-Lunar China reference
49 ranges and osteoporosis defined according to the WHO Task Group criterion of a spine or
50 femoral neck T-score < -2.5 [4]. For each anthropometric factor (weight, BMI or spine
51 thickness) participants were divided into three equal tertiles and the prevalence of
52 osteoporosis diagnosed by QCT or DXA evaluated for each tertile. For DXA measurements
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1 the prevalence of osteoporosis was re-evaluated after spine and femoral neck BMD values
2 were adjusted for weight, BMI or spine thickness to their average value in men and women
3 respectively. Results for the different tertiles were compared in a 3 x 2 contingency table
4 using Fisher's exact test. To further evaluate the effects of adjusting DXA aBMD values,
5 QCT vBMD measurements of participants were plotted against DXA spine T-scores, femoral
6 neck T-scores and the lower of the two T-scores. The correlation coefficients for each sex
7 were evaluated before and after adjustment for weight, BMI and spine thickness and the
8 statistical significance of the difference between the two correlation coefficients determined
9 [24]. A P-value < 0.05 was taken to be statistically significant.
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23 **Results**

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26 A total of 964 men and 682 women received QCT and DXA lumbar spine bone density
27 measurements. Of these, 635 men and 402 women also received DXA hip measurements.
28 Table 2 gives the participants' descriptive statistics.
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34 Figure 1A shows the scatter plot of DXA spine Z-score against age for men. Points
35 plotted in red for the men >70 years old included a number of individuals with high Z-scores
36 suggestive of spinal degenerative disease, and these individuals were removed from further
37 analysis. For the men <70 years the mean Z-score and the slope of the regression line of Z-
38 score against age were both zero. Plots of Z-score against age for women and for QCT and
39 hip DXA in men did not show any similar anomaly.
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50 Figure 1B shows the scatter plot for DXA spine Z-score against body weight for the
51 men <70 years old in Figure 1A together with the linear regression line (solid red line) and
52 95% confidence interval (dashed red lines). The slope and standard error were $0.0393 \pm$
53 0.0038 Z-score units per kg. Similar results with slopes 8 to 10 times greater than the standard
54 error were found for the other DXA measurements. However, slopes of Z-score against
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1 weight for spine QCT in men ($P = 0.82$) and women ($P = 0.30$) were not significantly
2 different from zero. Findings for plots of QCT and DXA Z-scores against BMI and spine
3 thickness were similar to those for weight (Figures 1C,D).
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8 Figures 2A-C compare the slopes of the QCT and DXA Z-score regression lines in men
9 and women at the different measurement sites for the three anthropometric factors together
10 with their 95% confidence intervals (CI). In Table 3 the same slopes are listed in BMD units
11 (for example g/cm^2 per kg instead of Z-score units per kg) together with the values of the
12 population SD used to convert Z-scores into BMD units.
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21 Figure 3 shows the mean Z-score in each 10 kg interval of body weight plotted against
22 mean weight for the QCT spine and DXA spine and femoral neck sites in men and women
23 respectively. The error bars show the 95% CI. In each plot the red line is the linear regression
24 line evaluated as shown in Figure 1B. For each BMD site the results of the chi-squared test
25 show that the regression line is a good fit to the data points. Results for the total hip site (not
26 shown) were similar to the femoral neck.
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37 The percentages of men and women aged 50 years and over with osteoporosis in each
38 tertile of body weight, BMI and AP spine thickness are plotted in Figures 4A-C respectively.
39 Each panel of Figure 4 compares the prevalence of osteoporosis in each tertile for QCT
40 vBMD (left-hand set of three points), conventional DXA aBMD (middle set of three points),
41 and DXA aBMD adjusted for the respective anthropometric factor (right-hand set of three
42 points). Error bars show the 95% CI. DXA aBMD measurements were adjusted to the mean
43 value of the anthropometric factor in each sex. Further details including the adjustment factors
44 are given in the caption to Figure 4. The overall prevalence of osteoporosis diagnosed by
45 QCT was 16.3% in women and 5.4% in men, and for DXA was 15.6% in women and 3.0% in
46 men. When women were broken down into tertiles of body weight the prevalence of
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1 osteoporosis as diagnosed by QCT was independent of weight ($P = 0.89$), while for
2 conventional DXA there was a statistically significant trend for the prevalence of osteoporosis
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4 to decrease at higher weights ($P = 0.026$) that was no longer significant after adjusting aBMD
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6 values for weight ($P = 0.31$). The number of men with osteoporosis was too low for any of the
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8 differences to be statistically significant. The findings for tertiles of BMI and spine thickness
9
10 were similar (Figure 4B,C). When the highest and lowest tertiles were compared using 2 x 2
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12 contingency tables the P-values of the unadjusted vs. adjusted DXA results were 0.013 vs.
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14 0.29, 0.0019 vs. 0.29 and 0.019 vs. 1.0 for weight, BMI and spine thickness respectively.
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20 When the correlation coefficients of DXA spine T-score, femoral neck T-score and the
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22 lower of the two T-scores against QCT spine vBMD were plotted for men and women before
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24 and after adjustment for anthropometric factors there was a trend for the correlation
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26 coefficients to increase after adjustment and half the increases were statistically significant (P
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28 < 0.001) (Figure 5).
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34 **Discussion**

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37 This study aimed to investigate the influence of anthropometric factors such as body
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39 weight, BMI and AP spine thickness on the diagnosis of osteoporosis by QCT and DXA in a
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41 large cohort of healthy Chinese subjects. The overall prevalence of osteoporosis was similar
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43 in both sexes whether it was diagnosed by QCT or DXA. However, when participants were
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45 divided into tertiles of weight, BMI or spine thickness the prevalence of osteoporosis
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47 diagnosed by QCT was consistent across all three tertiles, while for DXA there were
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49 pronounced gradients with subjects with lower weight, BMI or spine thickness having a
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51 higher prevalence of osteoporosis compared with those with larger values. When DXA
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53 measurements were adjusted for weight, BMI or spine thickness using slopes of regression
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55 lines like those shown in Figure 1 the prevalence of osteoporosis was reduced in the lower
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tertile and increased in the higher tertile and findings were more consistent with those for QCT. There was also a trend for adjusted DXA T-scores to correlate more strongly with QCT vBMD, and in half the correlations the increases were statistically significant.

DXA uses attenuation measurements at two X-ray photon energies to minimise the influence of different soft tissue thickness and body composition over the scan area on the accuracy of aBMD measurements [25]. DXA aBMD measurements are the product of the average volumetric BMD and AP bone thickness in each pixel averaged over the bone region of interest (ROI). As such, measurements are sensitive to bone size as well as the true volumetric BMD making it more complicated to interpret results in children compared with adults and explaining some of the differences in reference ranges between men and women and between different ethnic groups. In contrast, QCT measures the true volumetric BMD independently of bone size or the thickness and composition of extraosseous soft tissue. The dependence of DXA aBMD on AP bone thickness and inhomogeneity in body composition may explain the striking differences compared with QCT in the correlation coefficients in Table 1 and slopes in Figure 2. The slopes of the regression lines with body weight in Figure 2A are similar for the spine and hip sites and between men and women. This suggests that a variation of bone size with body weight may be a factor in explaining the weight correlations found for DXA. Another explanation might be the increased stresses put on bone in heavier individuals, although it is notable that the absence of any effect on QCT measurements excludes an effect of body weight on spinal trabecular vBMD. A third explanation might be that in heavier individuals there is a systematic difference in the thickness of adipose tissue (AT) between the bone and soft tissue reference ROIs [14-16] and the effect of increasing BMI on aBMD is a soft tissue measurement error rather than a real difference. Tothill et al. estimated that 10 mm of AT thickness was equivalent to -0.043 g/cm^2 of hydroxyapatite[14], meaning that the slope of the aBMD regression lines with body weight in Table 2 could be

1 explained by AT thickness differences of 11 to 15 mm per 10 kg increase in body weight.
2 Further investigations of this issue could include direct measurements of bone sizes using CT
3 images, a comparison of integral aBMD in the hip measured with QCT compared with DXA,
4 or measurements of adipose tissue thickness and its variation with BMI using CT or MRI
5 imaging.
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13 Carter et al. were the first to compensate for differences in bone size by dividing aBMD
14 by the square root of the projected area to give an estimate of volumetric BMD referred to as
15 bone mineral apparent density (BMAD) [13]. Unlike QCT and DXA BMD measurements,
16 there is no accepted threshold for the diagnosis of osteoporosis using BMAD. For this reason
17 we used the DXA AP spine thickness defined as the square root of the average projected area
18 of the L2-4 vertebrae as an anthropometric factor predicted to correlate with DXA spine
19 aBMD. Mean value of L2-4 BMAD for the study participants was 0.28 g cm^{-3} in men and
20 0.29 g cm^{-3} in women, comparable to the spine aBMD adjustment factor of 0.23 g cm^{-3}
21 inferred from the scatter plots (Table 3). Unsurprisingly, the bone thickness inferred from
22 spine DXA measurements did not correlate as well with aBMD measurements made in the
23 hip (Table 1 and Table 3).
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41 Recently, Liu et al. proposed the use of weight corrected bone mineral content (wBMC) in the
42 spine and hip obtained by dividing the BMC in each ROI by body weight [wBMC =
43 BMC/weight (g/kg)] so that body weight rather than projected area is used for BMC
44 standardisation [20]. They showed that defining osteoporosis in terms of wBMC T-scores
45 removed the trend with conventional DXA aBMD for a greater proportion of patients in the
46 lower tertile of body weight to be diagnosed with osteoporosis than those in the upper tertile,
47 resulting in a more even distribution of diagnoses across the full range of body weights
48 similar to that for QCT in Figure 4 of the present paper. Our use of the slopes of the
49 regression lines of anthropometric factors to adjust DXA aBMD measurements had a similar
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2 effect in re-balancing the prevalence of osteoporosis, ensuring a more equal spread of
3 diagnoses and greater consistency with QCT.
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5 The findings of Liu et al. [20] and the difference between QCT and DXA in the
6 distribution of cases of osteoporosis across the range of body weights raises the question of
7 whether there is any justification for the goal of levelling out diagnoses of osteoporosis across
8 different body weights, or whether the present bias with DXA that directs anti-fracture
9 therapies preferentially towards lower weight patients achieves the best overall clinical
10 outcome. Since the aim of fracture prevention is paramount, this is an issue that can only be
11 decided using fracture data. There is evidence that, despite greater soft tissue mass and
12 thickness, obesity is not protective against fracture, particularly at the spine and appendicular
13 skeletal sites [17-19]. A recent study in Shanghai, China, reported that the prevalence of
14 vertebral deformity in men was similar to that in women (17% vs. 17.3%) over 60 years [26]
15 and a three-fold higher vertebral fracture prevalence in men has been reported elsewhere [17].
16 The application of a body weight or BMI correction for DXA BMD measurements may
17 improve the identification of people at risk of fracture, especially in obesity, which has been
18 identified as a risk factor for falls in men [27]. The fact that QCT vBMD is not associated
19 with body weight indicates that heavier weight does not have a beneficial effect on spine
20 trabecular vBMD, suggesting it may not be protective against fracture. Our findings suggest
21 that the ability of weight, BMI or spine thickness corrected aBMD to predict fracture risk
22 warrants further investigation.
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50 Our findings may have further relevance. The WHO diagnostic criteria for osteoporosis
51 and osteopenia were developed and validated on data for postmenopausal women and then
52 extended to men without the same rigorous validation seen in women. One consequence is
53 that the prevalence of osteoporosis in men may be higher than that currently projected by
54 WHO T-scores at around one-fifth the rate in women [3]. The mean weight of men in our
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1 study was 13 kg heavier than women, and adjustment of men's results to the mean body
2 weight in women may re-dress this imbalance. Our findings may have relevance for the
3 longitudinal monitoring of aBMD, particularly in populations where large changes in body
4 weight are expected, such as in patients undergoing bariatric surgery, in cancer patients after
5 chemotherapy and in children [28-32]. The rapid decline in the BMD of these patients may
6 reflect more the influence of weight loss on the aBMD measurement than their true bone loss,
7 especially given that QCT assessment of vBMD has demonstrated a negligible decline
8 compared with aBMD [29-32].
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20 Our study has several limitations. Firstly, this is a cross sectional study and no fracture
21 information was available. Therefore, it was not possible to compare the performances of raw
22 DXA aBMD, adjusted aBMD and QCT vBMD for predicting fracture risk. Further studies are
23 required into whether obesity is a protective factor against fractures and whether adjusting
24 DXA aBMD for anthropometric factors has a beneficial impact on the discriminative or
25 predictive power for vertebral fracture. Secondly, there were few men with osteoporosis. It
26 was necessary to exclude men over 70 years old from the DXA spine analysis because of the
27 high incidence of spinal osteoarthritis in these participants and their consequent elevated
28 BMD findings. Failure to exclude these men would have prejudiced the power of the study to
29 explore the relationship between body weight and spine aBMD.
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46 In conclusion, in this study we report that, after adjustment for gender and age, QCT
47 spine vBMD was not associated with body weight, BMI or spine bone thickness. In contrast,
48 after adjustment for gender and age, DXA spine and hip aBMD were strongly associated with
49 all three anthropometric factors. We determined adjustment factors for body weight of 0.005
50 $\text{g cm}^{-2} \text{ kg}^{-1}$ and 0.006 $\text{g cm}^{-2} \text{ kg}^{-1}$ for men and women respectively, for BMI of 0.013 g cm^{-2}
51 $\text{kg}^{-1} \text{ m}^2$ in both sexes, and for spine thickness of 0.23 cm^{-1} for spine aBMD and 0.15 cm^{-1} for
52 hip BMD. The application of these coefficients to adjust DXA aBMD measurements can help
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1 rebalance the diagnosis and management of osteoporosis between patients with higher and
2 lower than average body size making DXA outcomes more consistent with QCT vBMD.
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4 **Further studies are required into whether adjusting DXA aBMD for anthropometric factors**
5 **has a beneficial impact on the discriminative or predictive power for vertebral fracture.**
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10 **Conflicts of interest:** Ling Wang, Limei Ran, Xiaojuan Zha, Kaiping Zhao, Yingying Yang,
11 Qing Shuang, Yandong Liu, Karen Hind, Xiaoguang Cheng and Glen M Blake declare that
12 they have no conflicts of interest.
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Tables

Table 1: Pearson correlation coefficients of body weight, body mass index (BMI), DXA spine (L2-4) thickness and height with QCT and DXA BMD Z-score

| | | Pearson Correlation Coefficient with Z-score† | | | |
|--------|---------------|---|-----------------|----------------------|-----------------|
| Gender | BMD site | Weight | BMI | DXA Spine Thickness‡ | Height |
| Men | DXA Spine | 0.322 (P<0.001) | 0.259 (P<0.001) | 0.261 (P<0.001) | 0.168 (P<0.001) |
| | DXA Fem Neck | 0.362 (P<0.001) | 0.275 (P<0.001) | 0.191 (P<0.001) | 0.220 (P<0.001) |
| | DXA Total Hip | 0.388 (P<0.001) | 0.347 (P<0.001) | 0.147 (P<0.001) | 0.151 (P<0.001) |
| | QCT Spine | 0.007 (P=0.82) | 0.025 (P=0.44) | -0.068 (P=0.035) | -0.023 (P=0.47) |
| Women | DXA Spine | 0.305 (P<0.001) | 0.217 (P<0.001) | 0.266 (P<0.001) | 0.171 (P<0.001) |
| | DXA Fem Neck | 0.399 (P<0.001) | 0.347 (P<0.001) | 0.213 (P<0.001) | 0.119 (P=0.017) |
| | DXA Total Hip | 0.406 (P<0.001) | 0.398 (P<0.001) | 0.241 (P<0.001) | 0.037 (P =0.50) |
| | QCT Spine | 0.040 (P=0.30) | 0.038 (P=0.32) | 0.068 (P=0.078) | 0.009 (P=0.82) |

†: Z-scores calculated after adjusting BMD for age and normalizing to the population standard deviation values listed in Table 3

‡: DXA spine thickness defined as $\sqrt{(L2-4 \text{ projected area}/3)}$

Table 2: Descriptive statistics of subjects (mean and SD)

| | Men | Women | P-value |
|--|---------------|---------------|-----------|
| N | 964 | 682 | |
| Age (y) | 50.8 (10.2) | 52.6 (10.5) | P < 0.001 |
| Weight (kg) | 70.3 (9.6) | 57.3 (8.1) | P < 0.001 |
| Height (m) | 1.68 (0.06) | 1.56 (0.06) | P < 0.001 |
| BMI (kg m ⁻²) | 24.8 (3.0) | 23.6 (3.2) | P < 0.001 |
| DXA Spine Area (L2-4) (cm ²) | 46.3 (3.9) | 39.4 (3.6) | P < 0.001 |
| DXA Spine Thickness (cm) | 3.93 (0.16) | 3.56 (0.16) | P < 0.001 |
| QCT vBMD L1-2 mg cm ⁻³ | 130.4 (31.4) | 126.2 (43.6) | P = 0.022 |
| DXA aBMD L2-4 g cm ⁻² | 1.124 (0.152) | 1.070 (0.180) | P < 0.001 |
| DXA aBMD femoral neck g cm ⁻² | 0.920 (0.134) | 0.858 (0.136) | P < 0.001 |
| DXA aBMD total hip g cm ⁻² | 0.984 (0.130) | 0.912 (0.140) | P < 0.001 |

BMI: Body mass Index. Among the men 1.5% were underweight (BMI < 18.5), 52.6% were normal (BMI 18.5-24.9), 40.5% were overweight (BMI 25-29.9) and 5.5% were obese (BMI 30-39). For women the percentages were 2.9%, 66.2%, 27.6% and 3.3% respectively.

Table 3: Anthropometric BMD corrections by gender and QCT or DXA BMD measurement site. Slopes for body weight, BMI and spine thickness are expressed in BMD units per kg, per kg m⁻² and per cm respectively

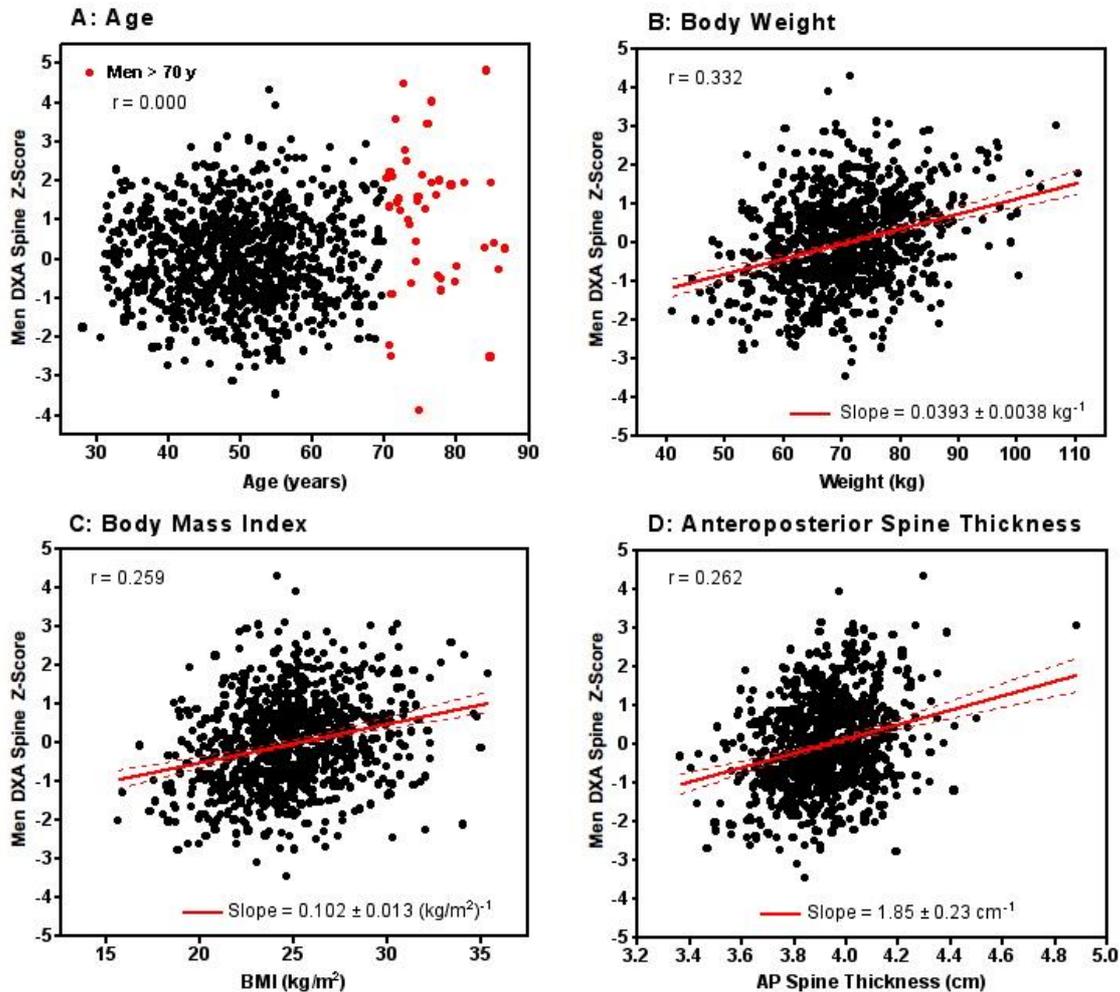
| Gender | BMD Site | Population SD (g cm ⁻²) | Body Weight Slope (SE)* (g cm ⁻² kg ⁻¹) | BMI Slope (SE)* (g cm ⁻² kg ⁻¹ m ²) | Spine Thickness Slope (SE)* (g cm ⁻³) |
|--------|------------------|-------------------------------------|--|---|---|
| Men | QCT Spine (L1-2) | 25† | 0.020† (0.087) | 0.216† (0.279) | -10.1† (5.1) |
| | DXA Spine (L2-4) | 0.12 | 0.0047 (0.0005) | 0.0122 (0.0015) | 0.223 (0.027) |
| | DXA Femoral Neck | 0.13 | 0.0046 (0.0005) | 0.0111 (0.0015) | 0.137 (0.028) |
| | DXA Total Hip | 0.13 | 0.0052 (0.0005) | 0.0157 (0.016) | 0.111 (0.030) |
| Women | QCT Spine (L1-2) | 25† | 0.135† (0.131) | 0.327† (0.331) | 11.6† (6.5) |
| | DXA Spine (L2-4) | 0.12 | 0.0056 (0.0007) | 0.0101 (0.0017) | 0.240 (0.034) |
| | DXA Femoral Neck | 0.12 | 0.0058 (0.0007) | 0.0125 (0.0017) | 0.156 (0.039) |
| | DXA Total Hip | 0.13 | 0.0063 (0.0008) | 0.0150 (0.0019) | 0.181 (0.040) |

* Slopes in BMD units obtained by multiplying the slopes in Z-score units plotted in Figures 1, 2 and 3 by the population SD in column 3.

† BMD units are in mg cm⁻³ rather than g cm⁻²

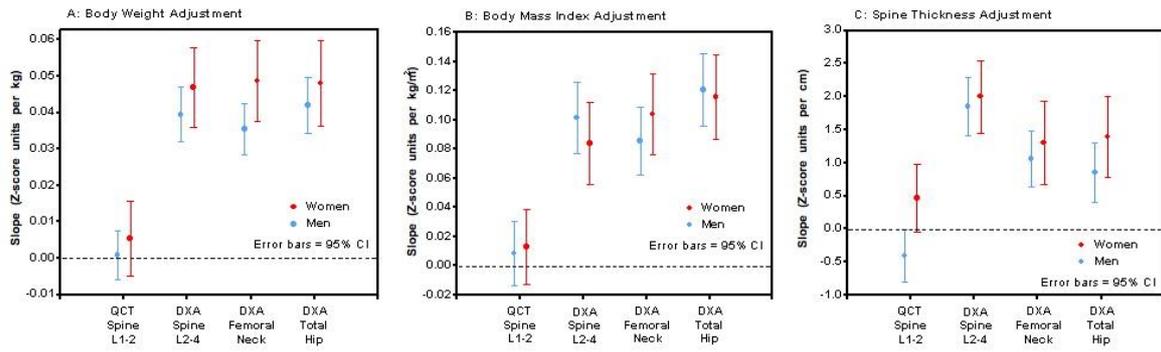
Figure Legends

Figure 1



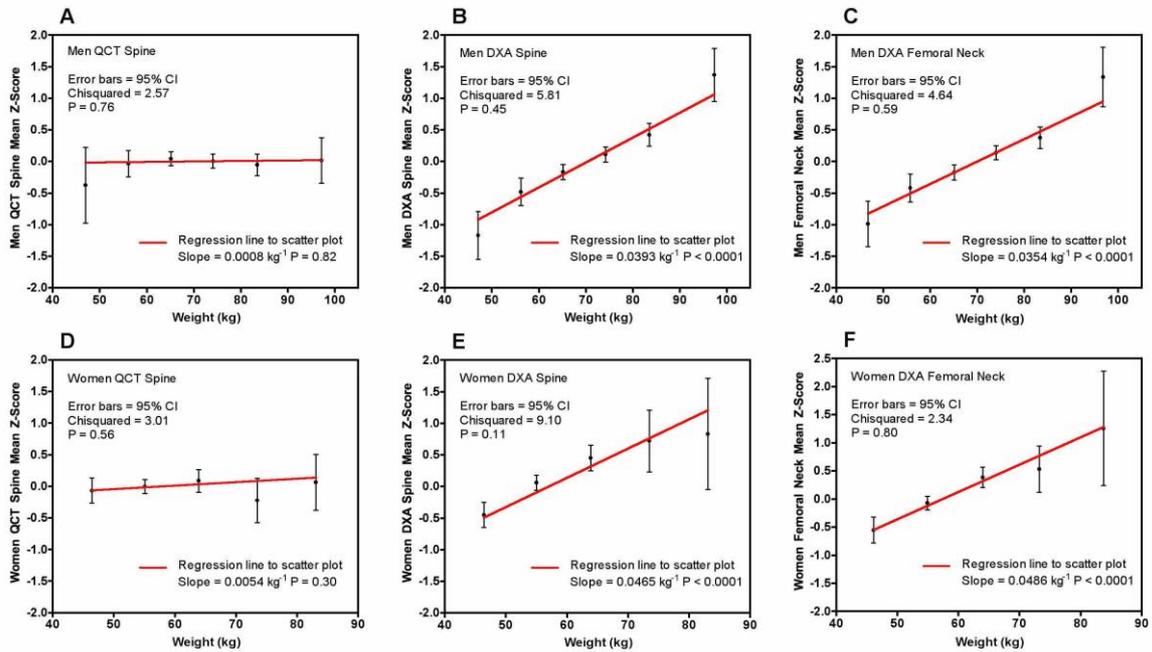
Scatter plots for men of DXA spine aBMD (L2-4) Z-score against: (A) age; (B) body weight; (C) body mass index (BMI); (D) anteroposterior spine thickness expressed as $\sqrt{(\text{L2-4 Area}/3)}$. Men over 70 years old plotted as red dots in (A) were excluded from the scatter plots in (B), (C) and (D) because of individuals with high Z-scores likely to be due to degenerative disease. The red continuous lines are the linear regression lines. Red dashed lines show the 95% confidence intervals. The slopes are expressed in Z-score units and the statistical error is ± 1 standard error.

Figure 2



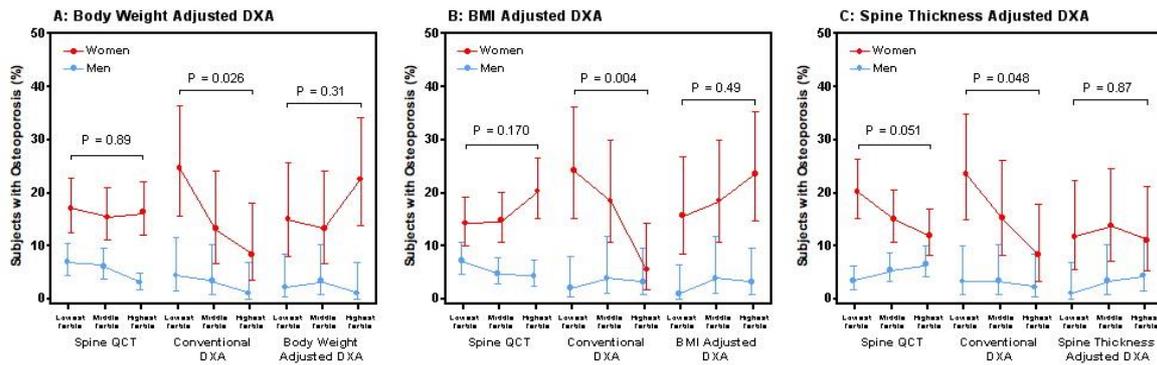
Slopes of Z-score against: (A) body weight; (B) BMI; (C) DXA AP spine thickness for QCT and DXA BMD measurements by gender and measurement site. Values plotted are the results of linear regression analysis similar to that shown for male spine DXA in Figures 1B-D. Error bars are the 95% confidence intervals.

Figure 3



Plots for men and women of mean Z-score in 10 kg intervals of body weight against mean body weight for that interval. Plots are for: (A) QCT spine (L1-2); (B): DXA spine (L2-4); (C) DXA femoral neck in men; (D) QCT spine (L1-2); (E): DXA spine (L2-4); (F) DXA femoral neck in women. Error bars show the 95% confidence intervals. The red lines are the linear regression lines obtained from scatter plots similar to Figure 1B. For each BMD site the results of the chi-squared test show that the regression line is a good fit to the data points

Figure 4



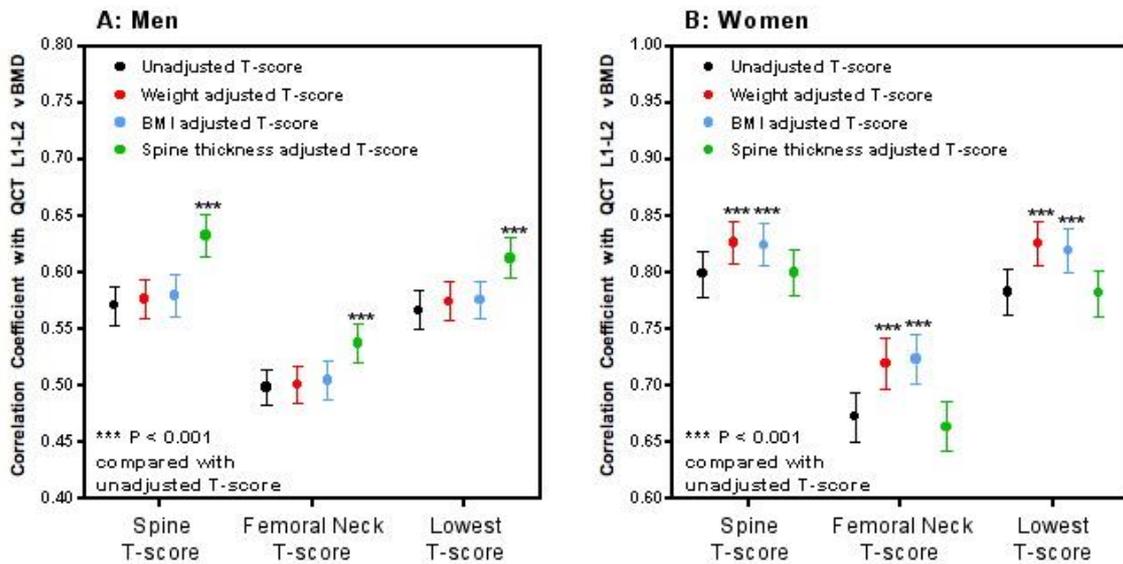
Percentage of women and men aged 50 years and over with osteoporosis plotted for tertiles of (A) body weight; (B) BMI; (C) AP spine thickness [= $\sqrt{(L2-4 \text{ Area}/3)}$]. In each panel the left-hand set of three points refer to QCT spine vBMD, the middle three points to conventionally interpreted DXA aBMD, and the right-hand three points to DXA aBMD adjusted for the respective anthropometric factor. Error bars show the 95% confidence intervals. For QCT, osteoporosis was defined as a mean trabecular vBMD in the L1-2 vertebrae $< 80 \text{ mg cm}^{-3}$. For DXA, osteoporosis was defined as a T-score at the spine (L2-4) or femoral neck $T < -2.5$. P-values are the statistical significance of the difference in each set of three tertiles in women evaluated using Fisher's Exact Test. None of the differences in men were statistically significant.

Body weight adjustment: spine and femoral neck DXA aBMD were adjusted to mean weights of 70 kg in men and 58 kg in women using corrections of $0.005 \text{ g cm}^{-2} \text{ kg}^{-1}$ and $0.006 \text{ g cm}^{-2} \text{ kg}^{-1}$ in men and women respectively. For men the lowest, middle and highest tertiles were 41.0-66.0, 66.1-73.9 and 74.0-110.5 kg respectively. In women they were 37.9-53.4, 53.5-59.6 and 59.7-95.5 kg.

BMI adjustment: spine and femoral neck DXA aBMD were adjusted to a mean BMI of 25.0 kg m^{-2} in men and 24.0 kg m^{-2} in women using a correction of $0.013 \text{ g cm}^{-2} \text{ kg}^{-1} \text{ m}^2$ in both sexes. For men the lowest, middle and highest tertiles were 15.6-23.9, 24.0-25.9 and 26.0-35.9 kg m^{-2} respectively. In women they were 14.9-22.8, 23.0-25.9 and 26.0-33.8 kg m^{-2} .

Spine thickness adjustment: spine and femoral neck DXA aBMD were adjusted to a mean thickness of 3.9 cm in men and 3.6 cm in women using corrections of 0.23 g cm^{-3} for spine BMD and 0.15 g cm^{-3} for femoral neck BMD in both sexes. For men the lowest, middle and highest tertiles were 3.36-3.88, 3.88-4.01 and 4.01-4.88 cm respectively. In women they were 3.17-3.53, 3.53-3.67 and 3.67-4.04 cm.

Figure 5



Plots of correlation coefficients of DXA spine T-score, femoral neck T-score and the lower of the two T-scores against QCT spine vBMD for: (A) men, and (B) women before and after adjustment for weight, BMI and spine thickness. Error bars show ± 1 SE for each correlation coefficient. P-values are the results of comparing adjusted and unadjusted T-scores after testing for the difference between two dependent correlations with one variable in common [25].