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Published in:
Journal of Clinical Densitometry

DOI:
[10.1016/j.jocd.2013.03.008](https://doi.org/10.1016/j.jocd.2013.03.008)

2014

[Link to publication](#)

Citation for published version (APA):
Callréus, M., McGuigan, F., & Åkesson, K. (2014). Country-Specific Young Adult Dual-Energy X-Ray Absorptiometry Reference Data Are Warranted for T-Score Calculations in Women: Data From the Peak-25 Cohort. *Journal of Clinical Densitometry*, 17(1), 129-135. <https://doi.org/10.1016/j.jocd.2013.03.008>

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3

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Country-specific young-adult DXA reference data are warranted for T-score calculations in women: Data from the PEAK-25 cohort

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Disclosures: NONE

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Abstract

The aims of this study were to provide normative data for dual energy X-ray absorptiometry (DXA) in 25 year old women and evaluate whether young adult Swedish women have bone mineral density (BMD) comparable to DXA manufacturer reference values and other equivalent populations. BMD at all sites was measured in the population-based PEAK-25 cohort (n=1061 women; age 25.5 ± 0.2). BMD values were standardized (sBMD) and compared against NHANES III and other cohorts. Based on the DXA manufacturer supplied reference values, Z-scores were 0.54 ± 0.98 (femoral neck; FN), 0.47 ± 0.96 (total hip; TH) and 0.32 ± 1.03 (lumbar spine; LS). In comparison to other studies, sBMD was higher in the PEAK-25 cohort (FN 1.5-8.3%), (TH 3.9-9.2%), (LS 2.4-6.5%) with the exception of TR-sBMD (trochanter) which was 2.5% lower compared to NHANES III. The concordance in identifying those in the lowest or highest quartile of BMD was highest between hip measurements (low 71-78%; high 70-84%), corresponding discordance 0-1%. At this age the correlation between DXA sites was strong ($r=0.62-0.94$). BMD in Swedish young adult women is generally higher than has been reported in other equivalently aged European and North American cohorts and suggests that that the high fracture incidence in Sweden is not explained by lower peak bone mass. The use of non-regional specific DXA reference data could contribute to misdiagnosed osteoporosis in elderly women.

Keywords: Bone mineral density, normative data, dual energy X-ray absorptiometry, young adult women, T-score, Z-score

Introduction

Fragility fracture incidence varies around the world, with the highest occurrence in Scandinavia [1]. Bone mineral density (BMD) is a strong predictor of fracture risk; for every standard deviation BMD decrease, fracture risk is doubled [2]. Consequently, BMD measurements, which are age- and sex-specific, are the cornerstone in diagnosis and risk evaluation. For individual assessment, appropriate reference values from a geographically and ethnically relevant, healthy population are necessary.

Bone mass later in life partially depends on peak bone mass (PBM) attained in young adulthood and defined as the highest bone mass achieved through normal growth [3]. Peak bone mass is also used as a comparative denominator for BMD values as a diagnostic tool; the T-score is an expression of standard deviations of current BMD relative to young adult BMD. Operationally, osteoporosis is defined as T-score values below -2.5 [4]. The Z-score i.e. standard deviations based on mean BMD values from a population of the same age is another comparative measure. The T-score is primarily used to diagnose osteoporosis in postmenopausal women, while the Z-score is more relevant in the young and in premenopausal women [5].

Since fracture risk estimates are based on the relative score, it is imperative that the T-score is appropriate to the older population to which it is being applied. Since peak BMD is strongly influenced by age, sex, geographical location and ethnicity, it is necessary to establish relevant normative values of bone mass from which the relative scores are calculated [6-12]. In particular, it is important to evaluate the relevance of the NHANES III values, since they constitute the WHO diagnostic reference.

Fracture rates in Sweden are very high, although it is not known if this is a consequence of a generally lower peak bone mass or related to other risk factors contributing later in life. The aims of the present study were (I) to provide normative data for DXA, including concordance between measurement sites, in a population-based sample of women aged 25, an age closely representing peak bone mass; and (II) to evaluate whether young adult women from Sweden

have BMD comparable to the reference values supplied by the DXA manufacturers and to other comparable populations in the published literature.

Subjects and methods

Participants

The PEAK-25 cohort, recruited during 1999–2004, consists of 25-year old women living in Malmö, Sweden. A total of 2394 women were invited and 1166 (49%) agreed to participate. Pregnancy (current or during the previous 12 months) was an exclusion criteria for the study and after removing these individuals and three others who fell out with the age limit, the final number in the cohort was 1061 [13].

The study was approved by the Ethics Committee of Lund University and the Swedish Data Inspection Board. The study was performed according to the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participating subjects.

Dual energy X-ray absorptiometry (DXA)

Bone mineral density (BMD, g/cm²) was measured using dual energy X-ray absorptiometry (DXA, Prodigy, Lunar Corp., GE, Madison, Wisconsin, USA) and software versions 2.15–7.70 at total body (TB), femoral neck (FN), trochanter (TR), total hip (TH) and lumbar spine, L1–L4 (LS). BMD at L2–L4 is also reported (Table 3) for comparison with other studies. T- and Z-scores are reported for FN, TH and LS.

The Lunar Prodigy scanner provided T-scores and Z-scores from the built-in reference population. In addition we calculated our own Z-scores ($Z\text{-score}_{\text{calc}}$) using the PEAK-25 cohort as a reference population, according to the formula $Z\text{-score}_{\text{calc}} = (\text{BMD} - \text{BMD}_{\text{Exp}}) / \text{SD}_{\text{Exp}}$; where BMD_{Exp} and SD_{Exp} are the mean and standard deviation of BMD in our cohort. Following International Society for Clinical Densitometry (ISCD) guidelines [5], individuals with Z-scores $< -2\text{SD}$ were designated “below the expected range for age” and $> -2\text{SD}$ were “within the expected range for age”.

The DXA absolute precision errors (CV%) were 0.37% (TB), 0.90% (FN), 0.56% (TR), 0.50% (TH), 0.65% (L1-L4) and 0.70% (L2-L4). System stability was calibrated daily using a manufacturer-supplied phantom.

Comparisons of normative values

We compared the PEAK-25 BMD data with other studies reporting normative values for similarly aged women [7, 8, 10, 11, 14-18], using the entire comparative cohort or a subgroup meeting the age criteria (25y±1y). When mean age was unavailable, the age-range was calculated as (low+high/2), to be within age 24-26.

As individual BMD data was not available for the comparative cohorts, standardized BMD (sBMD) values were calculated using the formula $sBMD = \alpha + \beta \times BMD$ [19, 20]. Coefficients α and β are dependent on scanner type and sub-region of hip-BMD as detailed in the supplementary information. A similar approach was used for recalculation of SD ($SD_{recalc} = \beta \times SD$) [21].

Calculation of LS-sBMD used the formula $= \delta \times (LS-BMD - \epsilon) + 1.0436$ [22] developed for L2-L4 [22, 23], but applied here to L1-L4 [24]. The constants (δ and ϵ) are dependent on scanner type and SD recalculation was performed according to Genant et al [23]. See supplementary information. Standardized BMD is expressed as mg/cm² to distinguish it from the manufacturer-specific BMD (g/cm²) [25].

Comparative identification of high and low values

Understanding the concordance between DXA measured skeletal sites is important in identifying those with low BMD. To explore this, subjects with complete data (n=1021) were split into

quartiles and analyzed for classification agreement of subjects in the lowest and highest quartiles for each region of interest (ROI).

Statistical methods

SPSS v19.0 (SPSS Inc., Chicago, Illinois, USA) was used throughout. T-test was used to compare between-group differences and Pearson's correlation was used for analysis of continuous data. To evaluate differences in BMD between studies, the unpaired t-test was used, based on mean, SD and number of subjects. Significance was set at $p < 0.05$.

Results

Normative DXA and anthropometric data for the PEAK-25 cohort are presented in Table 1. Mean T-scores for FN, TH and LS, provided by the DXA-scanner, ranged from 0.31–0.61. The Z-scores were within a similar range. In this age group T- and Z-scores should be similar at all sites and while this was the case at the LS ($p=0.30$), T-score was significantly higher than the Z-score at the FN ($p<0.001$) and TH ($p<0.001$).

BMD Distribution

Figure 1 shows the BMD distribution at all sites and for visual comparison, the average NHANES III value (available only for the hip) recalculated to a corresponding Lunar value.

According to the DXA provided FN Z-score (based on its built-in reference population), none of the PEAK-25 subjects had FN-BMD below the “expected range for age”. Using the PEAK-25 calculated FN Z-score as reference ($Z\text{-score}_{\text{calc}} = 0.00 \pm 1.00$), seven subjects had FN-BMD below the expected range for age ($<-2SD$), with a similar prevalence for total hip and lumbar spine (Table 2).

Proportion with osteopenia and osteoporosis

Applying the WHO criteria for osteopenia and osteoporosis using T-scores (DXA) in this cohort of 25-year old women, three subjects were identified with osteoporosis at the spine (0.3%) and none were identified at the hip. T-scores representing osteopenia were identified at the LS (9.3%, $n=98$); FN (4.5%, $n=48$) and TH (4.8%, $N=49$).

Comparisons with other studies

The calculated, standardized BMD values in our cohort and the nine comparative studies [7, 8, 10, 11, 14-18] together with original BMD values are presented in table 3. The PEAK-25 data, compared to NHANES III, was higher at the FN (1.5%; $p=0.044$) and TH (5.4%; $p<0.0001$) but lower at the TR (-2.5%; $p=0.002$). Only in the NHANES III [14] and Paggiosi studies [11] was the TR-sBMD significantly higher than observed in the PEAK-25 cohort. Conversely, compared to Kroger et al, [18], PEAK-25 participants had significantly higher TR-sBMD (2.9%; $p=0.022$; $n=71$), while similar values were noted compared to other studies.

For the other sites and studies, PEAK-25 values were either non-significantly different or higher than those reported: FN-sBMD (1.5-7.5%), TH-sBMD (2.6-9.2%), LS (L1-L4) (4.7%) and LS2 (L2-L4) (3.4%-6.5%).

Concordance between measurement sites

The concordance in identifying subjects in the lowest and highest DXA quartiles at different measurement sites was generally high, 71–78% of the same subjects fell into the low BMD quartile at all 3 hip sites and 70–84% in the high BMD quartile. Discordant results at the hip were seen in <1%. The concordance between hip and spine was 53-60%, and discordance 3-4%. Correlations between the LS vs hip sites were lowest (0.62-0.74) and highest for TH-BMD vs TR-BMD ($r=0.92$).

Discussion

This study provides normative reference data for DXA measured BMD in Swedish women at the presumed age of peak bone mass in, to our knowledge, the largest population-based cohort of young adult women. This also makes the study highly suitable to assess the applicability of currently available reference values to diagnose osteoporosis from T-score. Furthermore, in comparison to both scanner provided reference values and other, albeit smaller studies, this study indicates that bone mass in young Swedish women is similar to or above the reported averages. This finding leads us to speculate that low peak bone mass may not be a key contributor to the high fracture rate in post-menopausal and elderly women in Sweden, rather that with age other individual and environmental factors influence reduced bone strength and fracture.

There are several other cohorts which have reported locally derived normative values [7-12, 14-18, 26], however the most widely used reference population by DXA manufacturers is the NHANES III [26]; with 971 subjects it represents ages 20–29 and includes men and women. The PEAK-25 cohort, with data based on more than 1000 twenty-five year old women, is likely to more accurately represent peak bone mass and consequently more relevant as a regional reference dataset.

T-score is expressed as standard deviations relative to BMD in a young adult population matched for sex and ethnicity, whereas Z-score is relative to a population matched for age (and in the case of Lunar DXA values, also adjusted for weight). Thus, as the PEAK-25 cohort is standardized for both age and sex, at an age where PBM is assumed to have been reached [27], it could be expected that the T-scores and Z-scores should be close to zero. For both cases our results were approximately 0.5 SD above the DXA reference population. One reason may be that the reference population in the Lunar scanner is not applicable to Scandinavian women. Similar findings have been reported by Noon et al [28] who raised concerns with applying US reference values for Z-score calculation in UK populations. Another possibility might be that the reference population is not sufficiently large for a variety of settings or alternatively, young Swedish women actually have higher BMD.

If such a discordance between T and Z-scores persists later in life, there may be a risk of under-diagnosing osteoporosis; a lower BMD in a population may be 'normal' in relation to the scanner provided reference values, while in reality, given the higher BMD of the local young-normative reference population, BMD would actually be considerably lower. This theory is reinforced when we calculate our own Z-score specifically based on the PEAK-25 cohort, with more subjects below

the expected range for age at all sites compared with the built-in reference population (NHANES III data).

This was also obvious when comparing T- versus Z-scores, especially at the femoral neck where T-score was almost 13% higher than the corresponding Z-score. This could be related to the reference population or to the inclusion of body weight in the Lunar Z-score calculations, which can create larger differences between T- and Z-scores [29].

Furthermore, our cohort was scanned using a Lunar Prodigy where T- and Z-scores were calculated using software versions some of which were before the use of NHANES III as the reference population [21]. This may contribute to the discrepancy between T- and Z-scores in our cohort i.e the T- and Z-scores values were positive for the trochanter whereas in comparison to the standardized values the PEAK -25 cohort was lower.

In general, these results, irrespective of the reason, indicate that we might diagnose disease based on questionable T-scores. Even Z-scores, which are recommended for the age of our population, call for use with discretion. Z-score calculation method is not standardized and differs between DXA manufactures, and concerns for its validity in clinical practice have been raised before [30].

Comparison of the published normative DXA values in different populations may help address whether the reference population used by the DXA scanner is relevant and how BMD in young Scandinavian women compares worldwide. Overall, BMD values in PEAK-25 were similar or significantly higher compared to similarly aged international cohorts [7, 8, 10, 11, 14-18]. This suggests that lower peak bone mass does not simply explain the observed high fracture incidence later in life.

Although FN-BMD is the preferred site for diagnosing osteoporosis in elderly women [5], it is useful to understand how it compares to other DXA regions in the young. At the femoral neck, the proportion of shared subjects reached 70–80% concordance for TR-BMD and TH-BMD, reflecting the high correlation between DXA measurements sites.

A considerable strength of this large population-based cohort is its design with a narrow age focus i.e. women aged 25, when bone accrual is regarded as being maximized. Also, our cohort uses a population-based approach, reducing the selection bias. Nevertheless, it is not known if our results are generalizable to other populations. Our study also has some limitations, one of which is the 49% response rate, although this is good for the age-group. To allow comparison with published cohorts, we rely on standardized BMD values, which may not fully account for

scanner-related differences. Nevertheless, the consistent finding of higher BMD in our cohort, regardless of scanning method, suggests that our results are accurate.

In summary, this study provides the first normative bone mass data for DXA in a large population-based cohort of Scandinavian women at the age of presumed peak bone mass. Our study suggests that BMD in Scandinavian women is generally higher than has been reported in other equivalently aged European and North American cohorts. The study also emphasizes the importance of using ethno-geographically appropriate reference data to discriminate osteoporosis versus normal bone mass.

Table 1 Descriptive data from the PEAK-25 cohort

Variables	N	Mean	Range
Age	1061	25.5 ± 0.2	25.0 – 26.0
Height (cm)	1060	168 ± 6	150 – 187
Weight (kg)	1060	64.7 ± 11.4	40.0 – 141.0
BMI (kg/m ²)	1060	23.0 ± 3.8	15.2 – 51.2
Menarche (years)	1052	12.7 ± 1.3	9 – 19
BMD (g/cm²)*			
Total body	1060	1.174 ± 0.073	0.969 – 1.486
Femoral neck	1057	1.053 ± 0.123	0.746 – 1.604
Trochanter	1057	0.830 ± 0.108	0.537 – 1.357
Total hip	1022	1.061 ± 0.121	0.742 – 1.593
Lumbar spine (L1–L4)	1059	1.217 ± 0.128	0.824 – 1.868
Lumbar spine (L2–L4)	1060	1.239 ± 0.131	0.842 – 1.885
T-score*			
Femoral neck	1057	0.61 ± 1.02	–1.95 – 5.20
Total hip	1022	0.50 ± 1.01	–2.15 – 4.94
Lumbar spine	1059	0.31 ± 1.07	–2.97 – 5.74
Z-score*			
Femoral neck	1057	0.54 ± 0.98	–1.77 – 4.27
Total hip	1022	0.47 ± 0.96	–1.92 – 4.75
Lumbar spine	1059	0.32 ± 1.03	–3.15 – 5.54

* Values obtained using Lunar Prodigy

Table 2 Proportion of subjects categorized according to standard deviations (SD) from the mean, calculated using the PEAK-25 cohort as the reference population. The scanner calculated Z-score of -2SD and below is included for comparison

Z-score	Femoral Neck (n=1057)			Total Hip (n=1022)			Lumbar Spine (n=1059)		
	BMD cutoff	N	%	BMD cutoff	N	%	BMD cutoff	N	%
>+2 SD	1.299	39	3.7%	1.303	33	3.2%	1.473	27	2.5%
+1 SD to +2 SD	1.176	133	12.6%	1.182	128	12.5%	1.345	140	13.2%
- 1 SD to + 1 SD	-	736	69.6%	-	710	69.5%	-	735	69.4%
-1 SD to -2 SD	0.930	142	13.4%	0.940	135	13.2%	1.089	140	13.2%
<-2 SD	0.807	7	0.7%	0.819	16	1.6%	0.961	17	1.6%
<hr/>									
*Z-score <-2 SD	–	0	0.0%	–	0	0.0%	–	12	1.1%

* Z-score obtained from the Lunar Prodigy DXA-scanner. -2 SD is the limit for 'expected range for age'

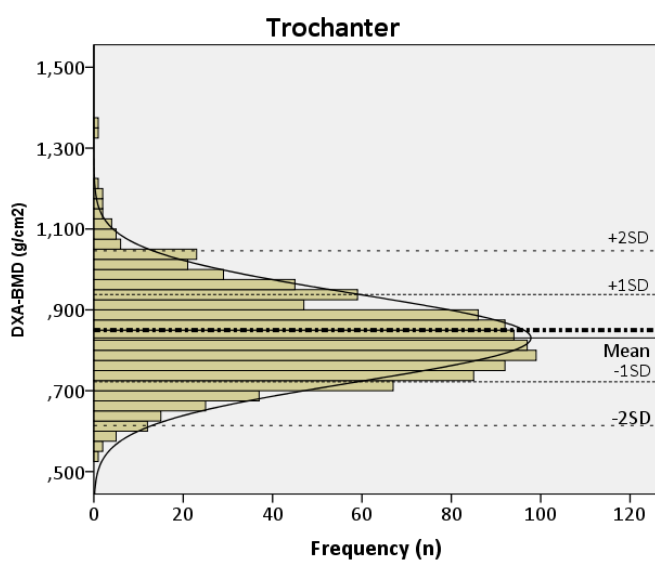
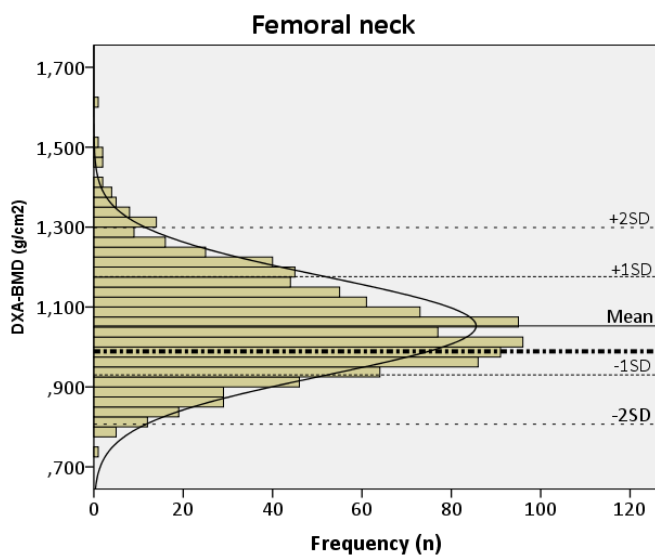
Table 3 Comparisons of the PEAK-25 cohort data with other studies reporting normative values for comparatively aged women

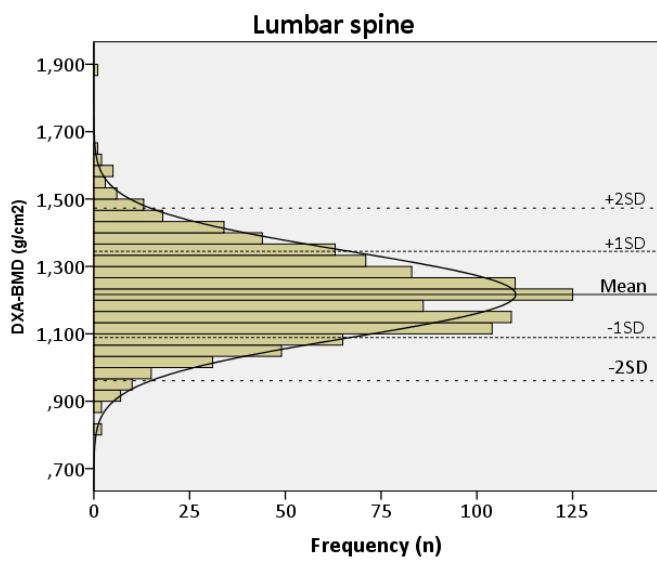
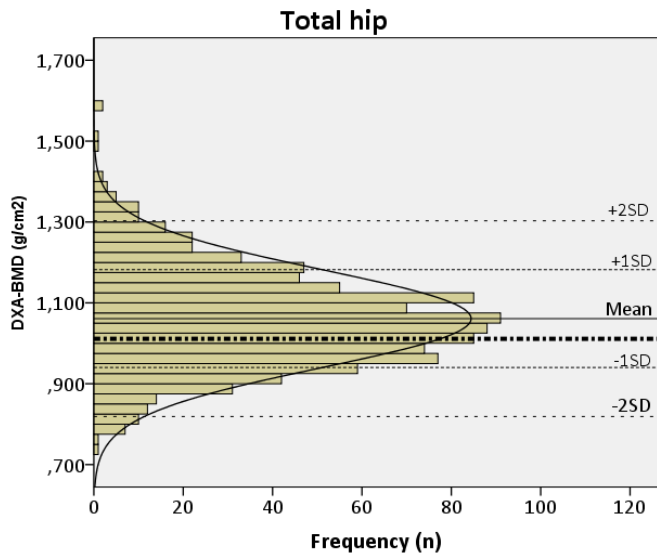
Study	Country	Age	N	Scanner		FN	TR	TH	LS (L1–L4)	LS (L2–L4)
PEAK-25	Sweden	25 (25.5)	1060	Lunar Prodigy	Scanner BMD	1.053 ± 0.123	0.830 ± 0.108	1.061 ± 0.121	1.217 ± 0.128	1.239 ± 0.131
					sBMD	966 ± 115	746 ± 102	1008 ± 118	1157 ± 122	1178 ± 125
NHANES III [14] 1998	USA	20–29 (NA)	409	Hologic QDR	Scanner BMD	0.858 ± 0.120	0.708 ± 0.099	0.942 ± 0.122	NA	NA
					sBMD	952 ± 130	765 ± 109	956 ± 123	NA	NA
					PEAK-25 vs Study	1.5% (0.044)	-2.5% (0.002)	5.4% (<0.001)	NA	NA
Paggiosi [11] 2011	Europe	20-29 (25.4)	104	Hologic QDR	Scanner BMD	0.859 ± 0.118	0.733 ± 0.101	0.968 ± 0.115	NA	NA
					sBMD	953 ± 128	793 ± 112	982 ± 116	NA	NA
					PEAK-25 vs Study	1.4% (NS)	-5.9% (<0.001)	2.6% (0.032)	NA	NA
Zhou [10] 2010	Canada	24 (24)	21	Hologic	Scanner BMD	0.848 ± 0.105	0.703 ± 0.101	0.979 ± 0.115	1.035 ± 0.126	NA
					sBMD	941 ± 114	760 ± 112	993 ± 116	1110 ± 136	NA
					PEAK-25 vs Study	2.7% (NS)	-1.8% (NS)	1.5% (NS)	4.2% (NS)	NA
Kaptoge [8] 2008	Europe	19–30 (25)	329	Hologic QDR	Scanner BMD	0.873 ± 0.135	0.695 ± 0.105	NA	NA	1.058 ± 0.130
					sBMD	968 ± 147	751 ± 116	NA	NA	1134 ± 140
					PEAK-25 vs Study	-0.2% (NS)	-0.7% (NS)	NA	NA	3.9% (<0.001)
Bachrach [15] 1999	USA	23–26 (NA)	57	Hologic QDR	Scanner BMD	0.873 ± 0.114	NA	0.956 ± 0.125	NA	1.074 ± 0.117
					sBMD	968 ± 124	NA	970 ± 126	NA	1151 ± 126
					PEAK-25 vs Study	-0.2% (NS)	NA	3.9% (0.019)	NA	2.3% (NS)
Mazess [16] 1999	USA	20–29 (NA)	30	Lunar DPX	Scanner BMD	1.102 ± 0.150	0.791 ± 0.110	1.000 ± 0.120	NA	1.242 ± 0.140
					sBMD	1012 ± 141	709 ± 104	948 ± 117	NA	1181 ± 133
					PEAK-25 vs Study	-4.5% (NS)	5.2% (NS)	6.3% (0.025)	NA	-0.3% (NS)
Hadjidakis [7] 1997	Greece	20–29 (NA)	33	Norland XR-26	Scanner BMD	0.923 ± 0.110	0.722 ± 0.120	NA	NA	1.033 ± 0.100
					sBMD	915 ± 108	751 ± 115	NA	NA	1106 ± 108
					PEAK-25 vs Study	5.6% (0.012)	-0.7% (NS)	NA	NA	6.5% (0.002)
Löfman [17] 1997	Sweden	20–29 (25.8)	27	Hologic QDR	Scanner BMD	0.810 ± 0.110	0.690 ± 0.100	0.910 ± 0.120	1.030 ± 0.130	NA
					sBMD	899 ± 120	745 ± 111	923 ± 121	1105 ± 140	NA
					PEAK-25 vs Study	7.5% (0.003)	0.1% (NS)	9.2% (<0.001)	4.7% (0.033)	NA
Kröger [18] 1992	Finland	20-29 (NA)	143	Lunar DPX	Scanner BMD	0.992 ± 0.130	0.808 ± 0.112	NA	NA	1.196 ± 0.126
					sBMD	908 ± 122	725 ± 106	NA	NA	1137 ± 104
					PEAK-25 vs Study	6.4% (<0.001)	2.9% (0.022)	NA	NA	3.4% (<0.001)

Mean age, when available is within parentheses. Scanner BMD is the scanner-specific BMD (g/cm²) reported as mean (SD). The recalculated standardized sBMD (mg/cm²) allows comparison between studies.

“PEAK-25 vs Study” is the % difference between sBMD’s in PEAK-25 vs the compared study; unpaired t-test p-values are in parentheses. NA=not available. NS=not significant.

Figure 1 Normality curves for the distribution of BMD values in femoral neck, trochanter, total hip and lumbar spine (L1-L4). The mean with 1SD and 2SD is marked in each figure. In the graphs for the hip variables, the bold dashed line represents the NHANES III mean value, recalculated to a Lunar BMD value [19,20] (FN=0.989, TR=0.850 and TH=1.011).





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