

Efficacy of weight adjusted bone mineral content in osteoporosis diagnosis in Chinese female population

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Abstract

Background: Areal bone mineral density (aBMD) applied for osteoporosis diagnosis unavoidably results in the missing diagnosis in patients with large bones and misdiagnosis in those with small bones. Therefore, we try to find a new adjusted index of bone mineral content (BMC) to make up shortcomings of aBMD in osteoporosis diagnosis.

Methods: In this multi-center epidemiological study, BMC and aBMD of lumbar spines ($n=5510$) and proximal femurs ($n=4710$) were measured with dual energy X-ray absorptiometry (DXA). We analyzed the correlation between the bone mass and body weight in all subjects including four age groups (<19 years, 20–39 years, 40–49 years, >50 years). And then the body weight was used for standardizing BMC (named wBMC) and applied for the epidemiological analysis of osteoporosis.

Results: The correlation of body weight and BMC is 0.839 to 0.931 of lumbar vertebra 1–4 (L_{1-4}), and 0.71 to 0.95 of femoral neck in different age groups. When aBMD was applied for diagnosing osteoporosis, the prevalence was 7.55%, 16.39%, and 25.83% in patients with a high, intermediate, and low body weight respectively. However, the prevalence was 21.8%, 18.03%, and 11.64% by wBMC applied for diagnosing osteoporosis. Moreover, the prevalence of osteoporosis increased by 3.76% by wBMC with the body weight increased by 5 kg. The prevalence decreased by 1.94% when the body weight decreased by 5 kg.

Conclusions: wBMC can reduce the missed diagnosis in patients with large body weight and reduce misdiagnosis in those with small body weight. Including children, wBMC may be feasible for osteoporosis diagnosis individuals at any age.

Keywords: Bone mineral content; Weight-standardized bone mineral content; Bone density; Dual-energy X-ray absorptiometry; Osteoporosis

Introduction

The diagnostic criteria for osteoporosis (OP) recommended by the World Health Organization (WHO) in 1994 was the areal bone mineral density (aBMD=BMC/projected bone area).^[1,2] In 1999, Duan *et al* reported that the bone mineral content (BMC) of the third lumbar vertebra body was positively correlated with bone volume, with a correlation coefficient of 0.79 and a regression equation of $BMC=2.38 + 0.29 \times \text{volume}$.^[3] To minimize the influence of bone volume on BMC, the bone size-standardized BMC is categorized into BMC (g) divided by the projected area of the region scanned (cm^2) and BMC (g) divided by bone volume (cm^3). Since bones are three-dimensional tissues, only volumetric bone mineral density (vBMD) can be regarded as completely standardized, hence the areal bone mineral density is incomplete. Carter

found that the bone thickness was not standardized when aBMD was applied.^[4] For example, for two bones of different sizes with the same vBMD, the application of aBMD results in the increased standardized aBMD in individuals with large bones and decreased aBMD in those with small bones. As a result, missed cases or misdiagnoses occur. There are two cubic bones with the same vBMD (1.0 g/cm^3) and with the different side lengths (0.5 cm and 2.0 cm, respectively), the BMC is 0.125 g and 8.000 g and the aBMD is 0.25 g/cm^2 and 4.00 g/cm^2 , respectively. Although the vBMD is the same (1.0 g/cm^3), the aBMD differs up to 16 times, which will ultimately result in missed or misdiagnosed cases. In conclusion, vBMD for OP diagnosis should really be taken into account. However, the most sophisticated dual energy X-ray absorptiometry (DXA) instrument is not able to

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detect bone volume *in vivo*. As a result, novel quantitative imaging techniques are being used to diagnose the OP, which include three-dimensional bone architecture with quantitative computed tomography (QCT), dedicated high-resolution (HR) CT, magnetic resonance imaging (MRI), and so on.^[5] However, their wild application is limited because of extra scanning, radiation and costs. Therefore, we prepared to explore a kind of simple, efficient, and reliable method for BMC standardization.

The weight-bearing function of the bones determines their morphologies and bone mass.^[6] The basic mechanical load of the bones is the gravity (the body weight). In other words, body weight is a key determinant of bone mass.^[7-10]

Based on the data of 4380 women from eight Asian countries, Koh *et al* found that body weight was a very important factor for predicting the risk of OP, and a simple tool named Osteoporosis Self-assessment Tool for Asia (OSTA) was developed. The formula of OSTA score is $(\text{Weight}-\text{Age}) \times 0.2$, and populations with an OSTA score ≤ 5 were regarded as at high risk.^[11] Lu *et al*'s study suggested that vBMD of cases from 5 years to 27 years old remained unchanged, with their body weight increased accordingly.^[12] In our previous study, we measured the whole bone mass of 114 male and female subjects (20–40 years) using DXA and found that the BMCs of the loading parts of the total body, trunk, and lower extremities were positively correlated with body weight (correlation coefficient: 0.847, 0.877, and 0.846, respectively).^[13]

With researches mentioned above indicated that body weight was a key determinant of bone mass,^[6-13] the standardization of BMC using body weight should be investigated. In this study, we analyzed the relationship between BMC and body weight, and then standardized BMC by body weight (named wBMC) in 5510 subjects from epidemiological survey. In addition, we further studied the role of wBMC in supplementing the shortcomings of aBMD and in predicting osteoporosis.

Methods

Inclusion and exclusion criteria

All the samples were provided by six centers located in the city of Beijing, Shanghai, Jiaying, Nanjing, Chengdu, and Guangzhou in China. The study received approval from ethics committee review board. All subjects voluntarily participated in the study and signed the consent form. All procedures were performed according to an Institutional Review Board (IRB)-approved protocol. Random cluster sampling was performed based on the environmental and economic conditions in Chengdu and Guangzhou. Subjects in Shanghai and Jiaying were mobilized by the community managers to attend the study, whereas subjects in Beijing and Nanjing were individuals who received health check-ups. The professions of these subjects were civil servants, workers, farmers, teachers, housewives, and students. The body weight of the minors changes dramatically, which provides useful clues for observing the relationship of BMC with the change of body weight and for index selection. Therefore, some minors were also included in this study. Only female subjects were enrolled in this study

according to the criteria for OP diagnosis of females established by Kanis *et al*.^[1] All subjects received questionnaire-based survey. Chronic parenchymal organ diseases and diseases that may affect bone metabolism including heart disease, kidney disease, liver disease, gastrointestinal disease, thyroid disease, parathyroid disease, adrenal disease, diabetes, and malignancy were excluded. Drugs (glucocorticoids, anti-epileptic drugs, fluoride-based preparations, bisphosphones, thyroxine, and estrogen replacement therapy) that may affect bone metabolism were also excluded.

BMD measurement

aBMD was measured using GE Lunar DXA scanner (GE Healthcare, Madison, WI, USA) at posteroanterior (PA) lumbar spine (L₁₋₄) in 5510 cases and at the proximal femur (neck, trochanter, and total femur) in 4710 cases. Quality controls were performed in accordance with the manufacturer-recommended procedures. A European spine phantom (QRM Company, Germany) was circulated in these six centers. In each center, the phantom was scanned ten times and then reset to its original position; the data were transmitted to the data management center for processing and analysis. The average coefficient of variation of the aBMD data measured at these six centers was $0.67 \pm 0.36\%$ (Mean \pm SD), with a range of 0.3% to 1.4%. The average aBMD measurement of the European spine phantom showed no significant difference among these six centers.

According to World Health Organization (WHO), the definitions of osteopenia and OP are based on the standard deviations (SD score) of the mean aBMD of young adults aged 20 to 39 years (YA aBMD), or based on T score, which is the difference between the measured aBMD and normal YA aBMD divided by the standard deviation of BMD of young adults aged 20 to 39 years (YA SD). $T\text{-score} = (\text{aBMD} - \text{YA aBMD}) / \text{YA SD}$.^[1,2]

The diagnostic criteria proposed by WHO are: normal: $T\text{-score} \geq -1$; osteopenia: $-1 > T\text{-score} > -2.5$; and osteoporosis: $T\text{-score} \leq -2.5$.^[1,2]

Standardized BMC by body weight

The BMC standardized for the projected area of the region scanned ($\text{aBMD} = \text{BMC}/\text{cm}^2$) which is recommended by WHO, has long been applied for OP diagnosis. However, aBMD easily resulted in missed diagnosis in patients with large bones and misdiagnosis in those with small bones when applied for OP diagnosis because the incompleteness of aBMD index. As bone is a three-dimensional tissue, only bone volume-standardized BMC ($\text{vBMD} = \text{BMC}/\text{cm}^3$) can be regarded as having been fully standardized,^[4] but the most sophisticated DXA is not able to measure bone volume *in vivo*. We studied that body weight had the highest correlation with BMC by correlation coefficients analysis from 5510 samples of six different centers in China in this study. Therefore, body weight was proposed for BMC standardization. We named it as $\text{wBMC} = \text{BMC} / \text{Weight (g/kg)}$, which means the bone mineral content in each kilogram of body weight.

The normal reference values and diagnostic thresholds of wBMC

The WHO diagnostic and grading criteria for OP were applied in the wBMC, in which the “abnormal bone mass” is based on the measurements in normal reference populations. The population of the peak bone mass (PBM) of wBMC is based on young subjects aged 20 to 39 years according to the normal reference values proposed by Kanis *et al.*^[1] Notably, the wBMC of the femoral neck has already reached its PBM during the growth and development stage (3–19 years), and begins to decline after 5 years subgroup. Therefore, it is better to use PBM as the normal reference value. The measured T-score = (subjects wBMC – PBM wBMC) / PBM SD.

Statistical analysis

Statistical analysis was performed using Matlab 6.5 and the statistical modules of Microsoft Office. Age was stratified by 5 years. The BMC, aBMD, wBMC, height, weight, and body mass index (BMI) at different parts of body are expressed as mean ± standard deviation (SD). The correlation coefficients between bone mass and physical examination indices were calculated. For BMC distributed based body weight (1 kg every piece), frequency analysis and normal distribution hypothesis test were performed for pieces contains a sample size larger than 100 (eg, 45, 60, and 70 kg), which showed that their BMCs were normally distributed, with a mean ± 1 SD accounted for 68% of the total sample. On this basis, the regression analysis was performed after the body weight pieces with a sample size smaller than ten were ruled out. The regression curves between body weight (1 kg every pieces) with the mean of BMC at L₁₋₄ and femur neck in each age group (<19 years, 20–39 years, 40–49 years and >50 years). The BMCs of L₁₋₄ and femoral neck were standardized for body weight for populations with a correlation coefficient (R²) > 0.6 in linear regression analysis. Meanwhile, the

prevalence of OP among subjects with different body weight were compared in terms of wBMC and aBMD.

Results

Basic conditions

The population was divided into different age groups by 5 years, and cross-sectional analysis was performed on the changes of three physical examination indices (height, weight, and BMI) and bone mass (BMC and aBMD) with age [Tables 1 and 2]. As shown in Table 1, the mean height increased by 44% from <9-year-old to the before adults (15–19 years), reaching 160.09 cm, the peak height of one’s life, with the highest and lowest height being 176 cm and 110 cm. The body height gradually decreased along with increasing age, and the total loss rate was 6.7% throughout life. The body weight increased by 2.6 times (from 18.59 kg to 50.73 kg) from <9-year-old to the before adults (15–19 years). The body weight reached its peak value (mean: 58.56 kg) appeared between 45 and 49 years, and then declined gradually with aging. The total loss rate was 13.66% throughout life, and therefore the body weight is the index with a total loss rate secondary to bone mass only. The mean BMI was 15.15 in the <9 years subgroup, which increased by 31.1% in the 15 to 19 years subgroup (19.85) and reached its peak (23.61–24.08) in the 50 to 79 subgroups. After the peak maintained for as long as three decades, it began to decrease with a relatively low total loss rate of 5.56%. Obviously, BMI does not change remarkably with age. The BMC and aBMD of L₁₋₄ were 12.926 g and 0.583 g/cm² in the <9 years subgroup and reached their peaks (59.149 g and 1.141 g/cm²) in the 30 to 34 years subgroup. Compared with the peak values, they decreased by 3.0% and 5.0%, respectively, in the 45 to 49 years subgroup. The total loss rates of these two indices were 33.29% and 31.98%, being the indices with the second largest total loss rate. The BMC and aBMD of the femoral neck were 4.624 g and 0.955 g/cm² in the 15 to

Table 1: The distributions of height, weight, BMI, L₁₋₄ aBMD and L₁₋₄ BMC in different age groups (N=5510).

Age (years)	n	Height (cm)	Weight (kg)	BMI (kg/m ²)	L ₁₋₄ aBMD (g/cm ²)	L ₁₋₄ BMC (g)
≤9	78	111.06 ± 10.87	18.95 ± 4.63	15.15 ± 1.12	0.5825 ± 0.0697	12.9269 ± 2.8955
10–14	30	148.20 ± 10.79	41.60 ± 9.29	18.73 ± 2.40	0.8386 ± 0.1284	32.9110 ± 10.7795
15–19	11	160.09 ± 4.37	50.73 ± 6.12	19.85 ± 2.70	1.0260 ± 0.1118	48.7077 ± 6.2669
20–24	94	160.54 ± 4.49	51.65 ± 5.37	20.30 ± 1.82	1.0817 ± 0.0977	54.0769 ± 6.6750
25–29	150	159.70 ± 5.16	52.61 ± 6.19	20.63 ± 2.23	1.1200 ± 0.1095	57.0414 ± 7.8421
30–34	230	160.40 ± 5.64	55.14 ± 6.32	21.50 ± 2.97	1.1411 ± 0.1104	59.1489 ± 7.8633
35–39	337	159.59 ± 6.26	55.31 ± 6.17	21.75 ± 2.50	1.1235 ± 0.1171	58.4584 ± 8.1721
40–44	428	159.82 ± 5.08	57.50 ± 6.62	22.52 ± 2.49	1.1242 ± 0.1285	59.3575 ± 9.7807
45–49	604	159.70 ± 4.83	58.38 ± 6.67	22.90 ± 2.49	1.0795 ± 0.1443	57.3411 ± 10.1389
50–54	782	157.57 ± 5.52	58.89 ± 8.29	23.72 ± 3.19	0.9971 ± 0.1476	51.2353 ± 9.9095
55–59	726	157.22 ± 5.70	58.51 ± 8.34	23.63 ± 2.87	0.9307 ± 0.1484	47.7284 ± 10.2559
60–64	679	155.94 ± 5.63	57.79 ± 7.85	23.76 ± 3.01	0.8903 ± 0.1514	44.9359 ± 10.0004
65–69	671	154.89 ± 5.53	57.79 ± 8.86	24.08 ± 3.41	0.8731 ± 0.1522	43.9629 ± 10.5569
70–74	434	153.41 ± 5.69	55.87 ± 8.95	23.73 ± 3.56	0.8438 ± 0.1569	41.5328 ± 11.0569
75–79	177	151.53 ± 6.81	54.24 ± 8.89	23.61 ± 3.49	0.8090 ± 0.1758	39.7281 ± 12.0856
80–84	65	149.37 ± 6.02	49.69 ± 9.11	22.29 ± 3.99	0.7638 ± 0.1466	36.1923 ± 9.6156
≥85	14	148.86 ± 5.26	50.57 ± 10.91	22.77 ± 4.52	0.7764 ± 0.1581	39.4548 ± 12.1009

Data were shown as mean ± standard deviation. BMI: Body mass index, BMC: Bone mineral content, aBMD: Areal bone mineral density.

19 years subgroup, which increased by 107.2% and 55.4% compared with those in the <9 years subgroup. Both of them reached their peak values in the 30 to 34 years subgroup. The total loss rate of BMC and aBMD of the femoral neck was 35.91% and 38.21% throughout life, being the indices with the largest loss rate. Interestingly, there was an extraordinarily high value (4.4268) of BMC in the 40 to 44 years subgroup, which may be due to sampling error [Table 2]. In our current cohort, young adults aged 20 to 39 years were used as the normal reference population, among whom the BMC of L₁₋₄ and femoral neck was 57.884 g ± 8.001 g and 4.252 g ± 0.580 g, respectively, and the aBMD was 1.123 ± 0.112 (g/cm²) and 0.924 ± 0.127(g/cm²), respectively.

Correlation of bone mass (BMC and aBMD) with body weight, height, and BMI

Before BMC is used for OP diagnosis, it must be standardized to enable the comparison among individuals.

Table 2: The distributions of femur neck aBMD and BMC in different age groups (N=5510).

Age (years)	n	Neck aBMD (g/cm ²)	Neck BMC (g)
≤9	15	0.6138±0.0824	2.2320±0.253
10-14	18	0.7843±0.0800	3.0511±0.295
15-19	3	0.9550±0.0144	4.6237±0.679
20-24	78	0.9109±0.1261	4.1543±0.515
25-29	13	0.9217±0.1129	4.2044±0.492
30-34	19	0.9308±0.1261	4.3567±0.574
35-39	33	0.9222±0.1346	4.2314±0.623
40-44	35	0.9181±0.1344	4.4268±0.882
45-49	50	0.9087±0.1374	4.2609±0.720
50-54	678	0.8679±0.1205	4.0022±0.77
55-59	645	0.8141±0.1217	3.7557±0.70
60-64	599	0.7640±0.1146	3.5410±0.71
65-69	572	0.7302±0.1144	3.4158±0.73
70-74	365	0.7017±0.1234	3.1304±0.66
75-79	151	0.6670±0.1230	3.0047±0.84
80-84	50	0.5994±0.0899	2.8291±0.55
≥85	12	0.5751±0.0606	2.7923±0.62

Data were shown as mean±standard deviation. aBMD: Areal bone mineral density, BMC: Bone mineral content.

Analysis on the correlation between bone mass (BMC and aBMD) and three physical examination indices (height, weight, and BMI) is helpful to screen the optimal index for BMC standardization. Firstly, we analyzed the correlation of BMC and aBMD with the three physical examination indices in young adults aged 20 to 39 years who are not affected by menopause and bone/joint degeneration.

Table 3 shows that, among these young adults, the correlation coefficients for BMC and body height, weight, and BMI ranged 0.295 to 0.494, whereas those for aBMD and body height, weight, and BMI ranged 0.110 to 0.335. Obviously, compared with aBMD, BMC had closer relationship with these three indices, particularly the correlation coefficient (0.494) for L₁₋₄ BMC and body weight. For the femoral neck, the relationship between BMC and these three physical examination indices was also closer than aBMD, particularly the correlation coefficient (0.445) for BMC and body weight. Therefore, body weight-standardized BMC was selected. However, the BMCs of both L₁₋₄ and femoral neck were only moderately correlated with body weight (0.494 and 0.445, respectively), and therefore body weight are not sufficiently justified for BMC standardization. Based on the requirement of statistics, we obtained higher correlation coefficients for BMC and body weight from the 45-, 62, and 80-year subgroups (R²=0.627, 0.571, and 0.592, respectively) from Table 1. The correlation of samples in the only-1-year range group was superior to that in 20 to 39 age group with large sample size, prompting that there are new methodologies warranting further investigation. As mentioned above, body weight is a key determinant of BMC. The BMCs of different subjects with the same body weight are inevitably different, if the absolute frequency is normally distributed, for samples with the mean ± 1 SD of BMC accounting for 68% of sample sizes, the correlation between average values of BMCs and body weight is justified. Body weight was divided into pieces by 1 kg for these 5510 cases. Analysis of the frequency distribution showed that three pieces of BMC samples (45, 60, and 70 kg) with sample sizes larger than 100 were normally distributed. Therefore, the conventional method was modified based on its correlation and regression with the mean value of BMC and body weight, and thus remarkably increased the correlation. Thus, this method is applied in this study.

Table 3: The Correlations among height, weight, BMI, L₁₋₄ aBMD, L₁₋₄ BMC, femur neck aBMD and BMC in the group which ages from 20 to 39 [Correlation coefficients (P values)].

Region	Height (P values)	Weight (P values)	BMI (P values)	L ₁₋₄ aBMD (P values)	L ₁₋₄ BMC (P values)	Neck aBMD (P values)	Neck BMC (P values)
Height	1.000 (1.00)	0.384 (0.00)	-0.169 (0.00)	0.110 (0.00)	0.408 (0.00)	0.093 (0.01)	0.323 (0.00)
Weight	0.384 (0.00)	1.000 (1.00)	0.836 (0.00)	0.335 (0.00)	0.494 (0.00)	0.267 (0.00)	0.445 (0.00)
BMI	-0.169 (0.00)	0.836 (0.00)	1.000 (1.00)	0.287 (0.00)	0.295 (0.00)	0.222 (0.00)	0.285 (0.00)
L ₁₋₄ aBMD	0.110 (0.00)	0.335 (0.00)	0.287 (0.00)	1.000 (1.00)	0.793 (0.00)	0.437 (0.00)	0.454 (0.00)
L ₁₋₄ BMC	0.408 (0.00)	0.494 (0.00)	0.295 (0.00)	0.793 (0.00)	1.000 (1.00)	0.376 (0.00)	0.509 (0.00)
Neck aBMD	0.093 (0.01)	0.267 (0.00)	0.222 (0.00)	0.437 (0.00)	0.376 (0.00)	1.000 (1.00)	0.747 (0.00)

BMI: Body mass index, BMC: Bone mineral content, aBMD: Areal bone mineral density.

Table 4: The regression equations and correlations between average values of BMC and body weights.

Age (years)	Number of samples	Lumbar spine 1–4 Regression equations	R^2	Number of samples	Femur neck Regression equations	R^2
3–19	119	BMC=0.935 W – 5.428	0.879	36	BMC=0.0782 W + 0.246	0.711
20–39	811	BMC=0.525 W + 29.386	0.857	740	BMC=0.0307 W + 2.585	0.859
40–49	1032	BMC=0.502 W + 28.605	0.839	794	BMC=0.0315 W + 2.476	0.718
≥50	3548	BMC=0.648 W + 7.610	0.931	3140	BMC=0.0384 W + 1.334	0.950
Total	5510	BMC=0.829 W + 1.015	0.924	4710	BMC=0.0392 W + 1.449	0.902

BMC: Bone mineral content.

Correlation and regression of body weight (1 kg every piece) with the mean of BMC

In Table 4 and Figure 1, the body weight had the optimal correlation with average values of BMC in each age group: the R^2 ranged 0.839 to 0.931 for the lumbar spine and 0.710 to 0.95 for the femoral neck; for postmenopausal women aged ≥50 years, the R^2 at L_{1–4} and femoral neck were 0.93 and 0.95, respectively, which were best among all the age groups. Therefore, body weight standardized BMC (wBMC) is feasible for all age groups.

In Table 5 and Figure 2, the wBMC of L_{1–4} was lowest at the age group <9 years (0.692), reaching its peak (1.090) in the 25 years subgroup, and then declined slowly with age increasing, with a total loss rate of 27.88% throughout life. The wBMC of femoral neck was 0.084 ± 0.012 at the age group <9 years, reaching its peak bone mass (0.081–0.093) in the 20 years subgroup, and then declined slowly with age increasing, with a total loss rate of 32.90% throughout life. With the young adults aged 20 to 39 years as the normal reference population, the (mean±SD) of wBMC was (1.071 ± 0.144) and (0.0787 ± 0.011) at L_{1–4} and femoral neck.

Comparison of wBMC and aBMD for OP diagnosis

In accordance with the OP diagnosis criteria recommended by WHO, the subjects' conditions can be divided into osteoporosis, osteopenia, and normal. Meanwhile, the sensitivity and specificity of each diagnostic index can be minimized.

Comparison of wBMC and aBMD for OP diagnosis

As shown in Table 6, there are 3548 subjects at L_{1–4} who were aged ≥50 years, among 1101 (31.03%) of 3548 subjects were diagnosed as OP by aBMD and 1089 of 3548 subjects (30.70%) were diagnosed by wBMC (T-score ≤ –2.5 for OP diagnosis). Obviously, the prevalence of OP diagnosed by these two indices were close. In this study, 3140 subjects at femoral neck were above 50 years old, among whom 497 (15.82%) were diagnosed as OP by BMD and 506 (16.11%) by wBMC. The prevalence of OP diagnosed by these two indices were also nearly the same. When applied for OP diagnosis, the sensitivity of wBMC was 71.80% for L_{1–4} and 63.7% for femoral neck and the specificity was 70.77% for L_{1–4} and 77.60% for femoral neck.

Influence of body weight on the prevalence of OP

As shown in Table 7 and Figure 3, when the bone size is not considered, the prevalence of OP at the L_{1–4} of 3548 subjects was 31.06% and 30.72% when diagnosed by aBMD or wBMC respectively, and the prevalence of OP at the femoral neck of 3140 subjects was 15.82% and 16.11% when diagnosed by aBMD or wBMC. Using the average body weight (57.5 ± 0.5 kg) as the baseline, subjects with a body weight larger than the baseline is called large-body-weight subjects, and those with body weight less than the baseline is called small-body-weight subjects. When aBMD was applied for OP diagnosis, the prevalence of OP was negatively correlated with body weight either at L_{1–4} or at femoral neck: the prevalence of OP at L_{1–4} was 20.77%, 32.86%, and 50.15% in subjects with large, intermediate, and small body weight, whereas that at the femoral neck was 7.55%, 16.39%, and 25.83%, respectively. On the contrary, when wBMC is applied for OP diagnosis, the prevalence of OP showed a positive correlation with the body weight either at L_{1–4} or at femoral neck, which showed precisely the opposite trend with aBMD prevalence: the prevalence of OP at L_{1–4} in large-, intermediate-, and small-body weight individuals was 34.64%, 27.86%, and 29.27%, showing a relatively flat curve. Nevertheless, the prevalence of OP at the femoral neck was 21.81%, 18.03%, and 11.64% in these subjects. As shown in Table 7, when the body weight increased by 5 kg, the prevalence of OP diagnosed by aBMD decreased by 4.2% and that by wBMC increased by 3.76%. when the body weight decreased by 5 kg, the prevalence of OP diagnosed by aBMD increased by 9.32% and that by wBMC decreased by 1.94%. In fact, wBMC showed similar effectiveness in diagnosing OP at L_{1–4}. Not fully standardized, aBMD (g/cm²) is two-dimensional and, could result in missed diagnosis in subjects with large bones and misdiagnosis in those with small bones. When wBMC is applied for OP diagnosis, such missed diagnosis or misdiagnosis may be avoided.

Discussion

Osteoporosis is a bone disease characterized by a decrease in bone mass and microarchitectural alterations which results in bone fragility and increased risk of fractures. It is a serious problem for elderly women worldwide.^[14,15] Recommended by WHO in 1994, aBMD has been widely used to diagnose osteoporosis. However, aBMD, only standardized two dimension for bone, could not be

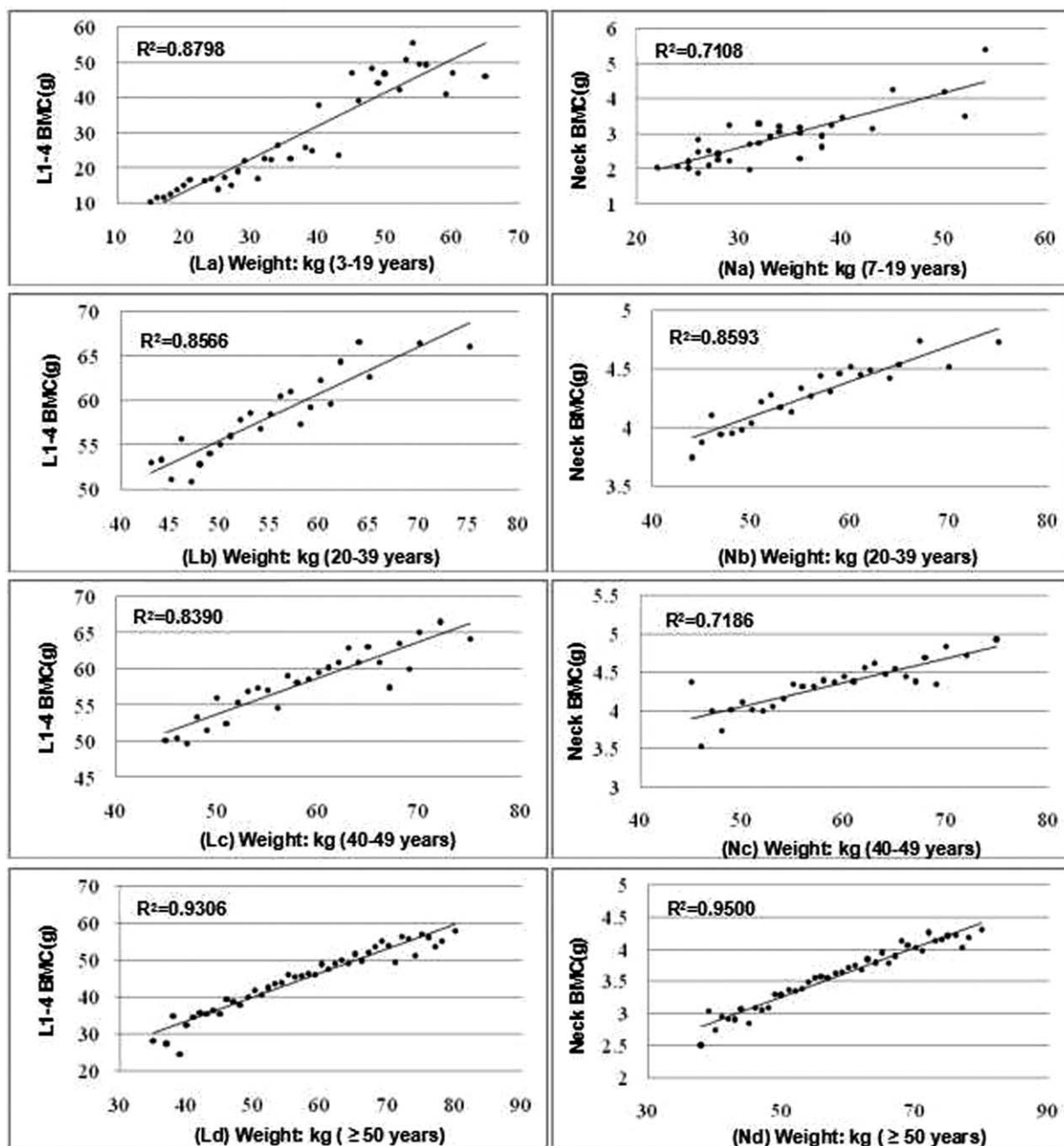


Figure 1: The regression curves between body weight (1 kg every pieces) with the mean of BMC at L₁₋₄ and femoral neck in each age groups. "W" refers to body weight.

regarded as completely standardized BMC because bones are three-dimensional tissues. The diagnosis for OP by aBMD result in the missed diagnosis in patients with large body weight and misdiagnosis in those with small body weight.^[16]

As the result, novel quantitative imaging techniques are being developed to evaluate osteoporosis including three-dimensional bone architecture with quantitative computed tomography (QCT), high-resolution (HR) CT, MRI, positron emission tomography (PET) and so on.^[5] However, their widespread use was limited because of additional scanning, radiation, and costs. Consequently,

we try to find out another simple and efficient and reliable way to diagnose osteoporosis.

Compton *et al* found that body weight was a key determinant of bone mass.^[7,8] Frost *et al* found that bone strain due to the change of mechanical loads will cause bone architectural and bone mass adaptations.^[17,18] Fracture from osteoporosis is associated with body weight-load, muscle strength, and ground-impact forces, among which the gravity (body weight) is the basis, the muscle strength is positively correlated with body weight (just as weightlifting and boxing athletes are grouped based on their body weights), and the ground impact force

Table 5: The distributions of wBMC at L₁₋₄ and femur neck in age groups (M±SD).

Age (years)	L ₁₋₄ wBMC (g/kg), n=5510	Neck wBMC (g/kg), n=4710
≤9	0.692±0.103	0.084±0.012
10-14	0.780±0.128	0.087±0.012
15-19	0.973±0.166	0.093±0.008
20-24	1.052±0.128	0.081±0.011
25-29	1.090±0.142	0.081±0.009
30-34	1.080±0.154	0.079±0.011
35-39	1.062±0.141	0.077±0.012
40-44	1.039±0.170	0.078±0.018
45-49	0.988±0.171	0.074±0.012
50-54	0.877±0.160	0.069±0.014
55-59	0.820±0.157	0.065±0.012
60-64	0.780±0.152	0.062±0.012
65-69	0.765±0.165	0.060±0.013
70-74	0.747±0.172	0.056±0.012
75-79	0.731±0.181	0.056±0.016
80-84	0.733±0.168	0.056±0.012
≥85	0.786±0.191	0.055±0.010

Data were shown as mean±standard deviation. wBMC: Weight standardized bone mineral content.

can be calculated using the following formula: $F = Mg \times \frac{h}{d}$, (in which the F represents a force that is opposed by a ground impact force of equal magnitude. Mg is the body weight, h is the height of an object dropped, and d is the distance between the touching of the ground and the stabilization of the center of gravity.) Therefore, when BMC is applied for OP diagnosis, it must be standardized to rule out the influence of other factors. It is meaningful to explore the optimal index for BMC standardization by investigating the correlations of several common mechanical load-related physical examination indices (body weight, body height, and BMI) with bone mass.

In our current study, we analyzed the correlations of bone mass (BMC and aBMD) with these three physical examination indices (body weight, body height, and BMI) in young adults aged 20 to 39 years. The bone mass during this period is highest throughout life and is least affected by adverse factors such as menopause and bone and joint degeneration. As shown in Table 3, the correlation coefficients between BMC at L₁₋₄ with body weight, body height, and BMI were 0.494, 0.404, and 0.295, respectively, and those between BMC at femoral neck with body weight, body height, and BMI were 0.445, 0.323, and 0.285. On the contrary, the aBMD at these two sites with these three physical examination indices were 0.335, 0.110, 0.287 and 0.267, 0.093, 0.222, respectively. Compared with aBMD, BMC had stronger correlation with these physical examination indices. Of these three physical examination indices, body weight had the optimal correlation with BMC (0.494 and 0.445). However, since such correlation was moderate, the body weight was not a perfect index for BMC standardization.

Therefore, further investigation on the correlation was warranted. Based on the requirement of statistics, we

obtained higher correlation coefficients for BMC and body weight from the 45 years, 62 years, and 80 years subgroups ($R^2=0.627, 0.571, \text{ and } 0.592$, respectively). Meanwhile, the small samples within every one year had better correlation coefficient than the larger sample size aged 20 to 39 years. Therefore, it can be speculated that the BMC of subjects at any age (every year) had relatively stronger correlation with body weight. Cheng *et al* also indicated that the aBMD at lumbar spine and proximal femur in subjects aged 20 to 89 years showed stable positive correlation with body weight ($R^2: 0.05-0.23$).^[14] Among subjects with BMC distributed according to body weight (1 kg every piece), pieces (45, 60, and 70 kg) with sample size larger than 100 were selected, and frequency analysis and normal distribution hypothesis tests were performed for the BMC of samples, which showed all the BMC were normally distributed, and BMC mean±1SD accounted for 68% of the sample size. Therefore, it is more reasonable to conclude that body weight (1 kg every piece) is correlated with the average value of BMC. As showed in Table 4, in the young adults aged 20 to 39 years, the correlation coefficient between body weight and the average value of BMC at the L₁₋₄ and femoral neck was 0.857 (BMC=0.525W + 29.23) and 0.859 (BMC=0.0307W + 2.585) respectively, showing better correlations than in Table 3. Subjects aged 3 to 94 years were divided into four age groups, and the correlation between body weight and the average value of BMC was analyzed, which showed that the R^2 at both L₁₋₄ and femoral neck ranged 0.710 to 0.950, prompting that body weight standardizing BMC is justified at any age [Table 4]. Since individuals with larger body weight have higher bone mass and those with smaller body weight have lower bone mass, person without bone mass appropriate with their body weight are more susceptible to OP. We previously measure the whole body bone mass with DXA in 114 male and female subjects aged 20 to 40 years in 2010, among whom the whole body BMC accounted for 3.84% and 3.98% of body weight, respectively.^[13] Liu *et al* measured the whole body bone mass and body weight using DXA continuously for three years among 375 subjects in 10-year-old girls, among whom the whole body BMC accounted for 4.0%, 4.0%, and 4.1% of body weight, respectively, in these three years.^[19] In both two studies, the percentages of whole body BMC in the body weight were around a constant. Thus, children adolescents, and young adults may share a normal reference value (at the femoral neck). By doing so, we may omit the difficulty in establishing a normal reference value for each year of age when using aBMD for OP diagnosis in children.

The body weight and bone volume have similar effectiveness for standardizing BMC

The BMC standardized for the projected area of the region scanned (aBMD=g/cm²) has long been applied for OP diagnosis, however, it leads to missed diagnosis in patients with large bone and misdiagnosis in subjects with small bone. In addition, although vBMD has undeniable advantages, the most sophisticated DXA instrument is not able to measure the bone volume *in vivo*. Therefore, we attempted to use body weight-standardized BMC (wBMC) to replace body volume-standardized BMC

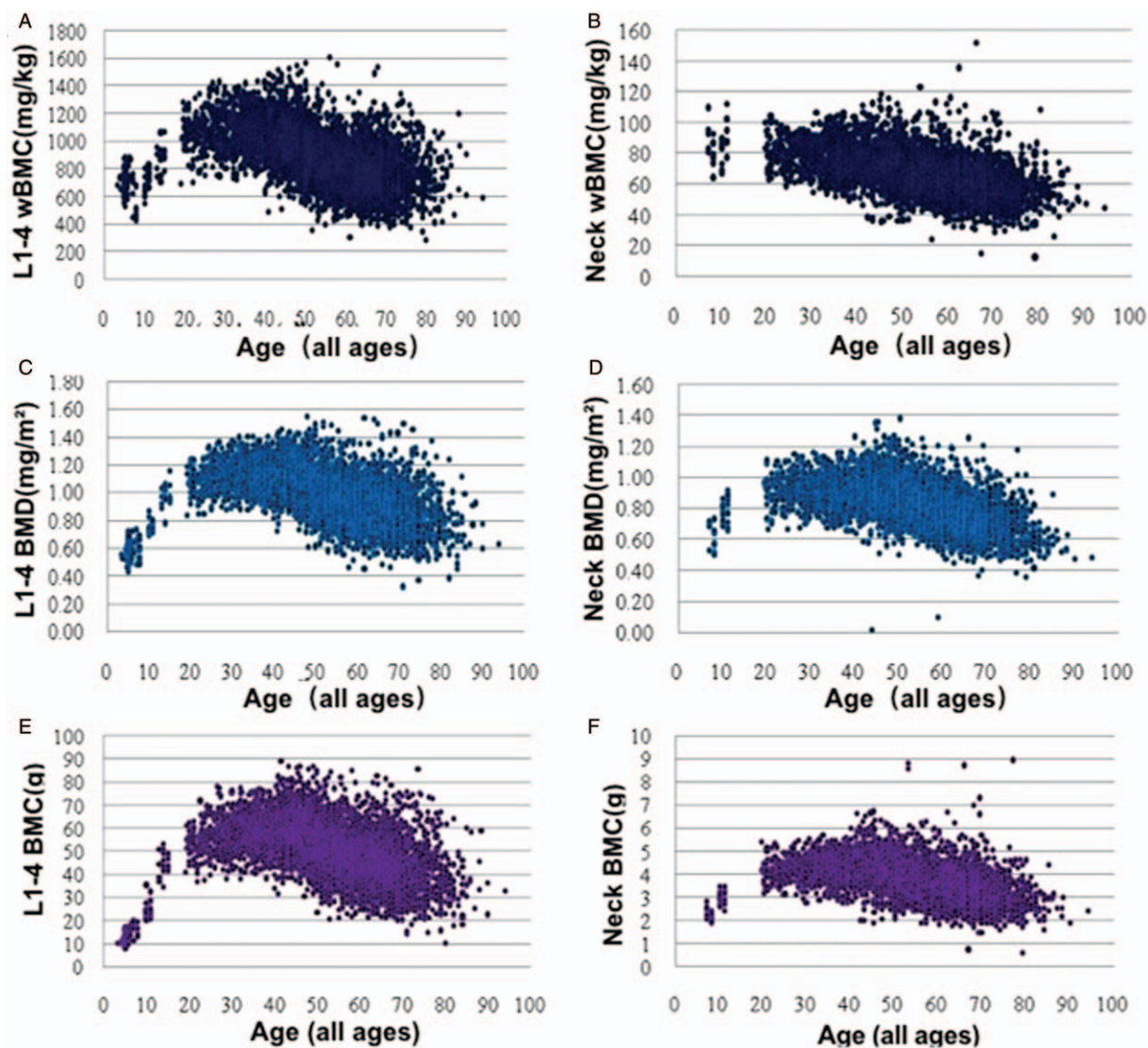


Figure 2: The scatterplots of wBMC/BMC/BMD at L₁₋₄ and femoral neck for all the samples in age orders (A-F).

Table 6: The detection rates of aBMD and wBMC for osteoporosis, osteopenia, and normal and the comparison of their sensitivity and specificity.

Region	n	Index of diagnosis	OP* n (%)	OPN* n (%)	Normal* n (%)	Sensitivity	Specificity
L ₁₋₄	3548	wBMC	1089 (30.70)	1656 (46.70)	803 (22.60)	71.82%	70.77%
		aBMD	1101 (31.03)	1469 (41.40)	978 (27.56)		
Femur	3140	wBMC	506 (16.11)	1596 (50.83)	1038 (33.05)	63.70%	77.60%
		aBMD	497 (15.82)	1369 (43.61)	1274 (40.57)		

aBMD: Areal bone mineral density; wBMC: Weight standardized bone mineral content; OP: Osteoporosis; OPN: Osteopenia; *: detection rate.

(vBMD). Lu *et al* in 1996 measured the BMC and bone volume in subjects aged 5 to 27 years old and found the vBMD of the femoral midshaft did not change with age or height in either sex,^[11] or, $BMC/volume = PBM$ (constant). However, the body weight increases by about three times from 5 years to 27 years, and the vBMD at the 5 years is not able to load the body weight at the 27 years of age. Therefore, the increased body weight must be loaded by the enlarged bone volume. It is thus speculated that, from the principles of mechanics of materials, body

weight (external force) is positively correlated with bone volume, and wBMC may have same effectiveness as vBMD.

Threshold values of wBMC normal reference value and their application

The normal reference value of wBMC is based on the measured value in young adults aged 20 to 39 years, and it is 1.071 ± 0.14 and 0.0787 ± 0.11 (mean \pm SD) at L₁₋₄ and

Table 7: Influence of the body weight (± 5 kg) on the prevalence of OP in subjects aged ≥ 50 years.

Weight			Prevalence of L ₁₋₄			Prevalence of FN	
Groups (kg)	± 5 kg	n	aBMD n (%)	wBMC n (%)	n	aBMD n (%)	wBMC n (%)
37.0	-20	133	107 (80.45)	42 (31.50)	78	42 (53.85)	8 (10.26)
42.0	-15	233	141 (60.52)	64 (27.47)	209	86 (41.15)	24 (11.48)
47.0	-10	482	240 (49.79)	141 (29.25)	431	110 (25.52)	47 (10.90)
52.0	-5	772	256 (33.16)	201 (26.03)	691	111 (16.06)	87 (12.59)
57.5 \pm 0.5	0	280	75 (26.79)	75 (26.79)	244	40 (16.39)	44 (18.03)
63.0	+5	768	166 (21.60)	227 (29.56)	666	66 (9.91)	118 (17.71)
68.0	+10	449	73 (16.26)	144 (32.07)	393	30 (7.63)	87 (22.14)
73.0	+15	248	23 (9.27)	89 (35.89)	204	12 (3.75)	47 (23.04)
78.0	+20	131	13 (9.92)	66 (50.39)	116	0	37 (31.90)
83.0	+25	72	6 (8.30)	41 (56.94)	19	0	7 (36.84)
(Sum)		3548	1100 (31.00)	1090 (30.72)	3140	497 (15.82)	506 (16.11)

57.5 \pm 0.5 kg is the average body weight group; OP: Osteoporosis; FN: Femoral neck.

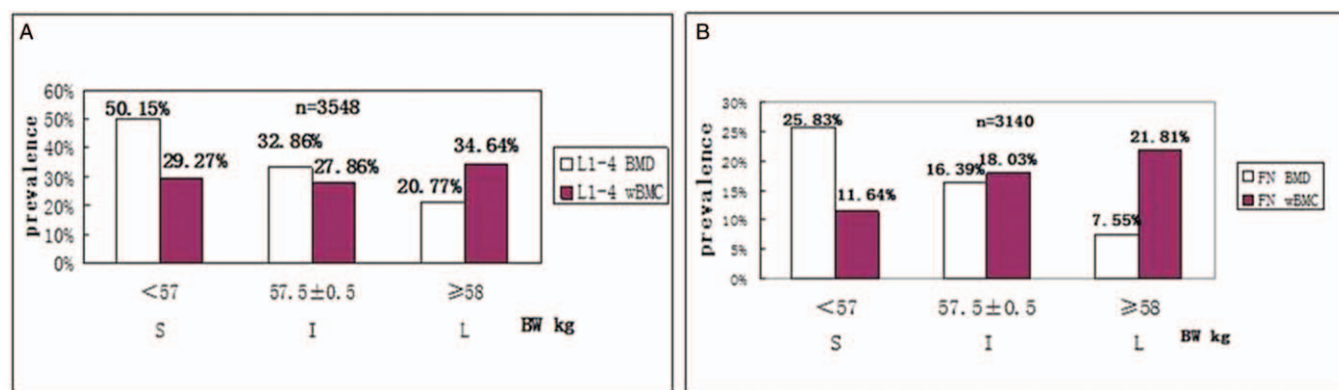


Figure 3: Influence of body weight (large, intermediate, and small) on the prevalence of OP at the L₁₋₄ (A) and at the femoral neck (B). S: Small; I: Intermediate; L: Large. BW: Body weight; FN: Femur neck; OP: Osteoporosis.

femoral neck. T-score = (measured wBMC - PBM wBMC) / SD. Based on the threshold values recommended by WHO, it can be applied for the diagnosis of osteoporosis (T score ≤ -2.5), osteopenia ($-1 >$ T score > -2.5), and normal (T score > -1.0).

The normal reference value of wBMC in young adults aged 20 to 39 years can be applied for OP diagnosis in adults. For children, the wBMC of the femoral neck has reached its peak bone mass and therefore the normal reference value for the adults could be applied for OP diagnosis in children. However, since the wBMC at L₁₋₄ is still lower than that of peak bone mass during the childhood in Table 5 and Figure 2, it cannot be used for OP diagnosis in children, and the underlying reasons still warrant further investigation.

In conclusion, wBMC, instead of aBMD, reduced the missed diagnosis in patients with large body weight and misdiagnosis in those with small body weight. However, this study has its own limitations for that the research population included in this study is only Chinese.

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Conflicts of interest

None.

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