The definition of spine bone mineral density (BMD)-classified osteoporosis and the much inflated prevalence of spine osteoporosis in older Chinese women when using the conventional cutpoint T-score of –2.5

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Osteoporosis is a systemic skeletal disease characterised by a reduction in bone mass and qualitative skeletal changes that cause an increase in bone fragility and a higher fracture risk. The clinical significance of osteoporosis lies in the fractures that occur, and the most important fracture is hip fracture. According to the 1994 World Health Organization (WHO) criteria, the T-score is defined as: $(BMD_{patient} - BMD_{young\ normal\ mean})/SD_{young\ normal\ population}$, where BMD is bone mineral density and SD is the standard deviation. When the femoral neck (FN) is measured in adult women, a cutpoint value of patient BMD of 2.5 SD below the $BMD_{young\ normal\ mean}$ satisfies that the prevalence of osteoporosis for those aged ≥50 years is about 16.2%, the same as the lifetime risk of hip fragility fracture (FF) (1,2). If other sites are also considered, this cutpoint value identifies approximately 30% of postmenopausal women as having osteoporosis, which is approximately equivalent to the lifetime risk of FF at the spine, hip, or forearm. It is widely assumed that this osteoporotic subset of the population loses bone mass at a faster rate, and interventions should ideally begin before an FF occurs.

While some clinics measure only FN BMD, others measure anteroposterior lumbar spine BMD and total hip BMD as well, with the site presenting the lowest T-score considered for the diagnosis of osteoporosis. However, the 1994 WHO document did not provide a specific definition of spine osteoporosis (1). Though primary osteoporosis is a systematic disease that affects the whole skeleton, it has been demonstrated that FN BMD reduction best predicts hip FF, and spine BMD reduction best predicts vertebral FF (3,4). Therefore, when both FN BMD and spine BMD are measured, it may be reasonably assumed that the clinical endpoint for spine osteoporosis is clinical vertebral FF. It is widely believed that the ratio of clinical vertebral FF to hip FF ratio is roughly 1 (5-7). In the study of Lam *et al.* (6) using data from Manitoba, Canada (2000 to 2007), for the female age group of 55–84 years, there were 2,313 clinical vertebral FFs and 2,395 hip FFs. The younger subjects (<70 years) had a higher prevalence of vertebral FF and older subjects (>70 years) had a higher prevalence of hip FF. The ratio of clinical vertebral FF to hip FF is close to 1 around the age of 70 years (*Figure 1*) (6,7). However, the reported prevalence of clinical vertebral FF is likely affected by the ease of access to medical care, with populations with easier access reporting a higher prevalence. If we use a T-score of –2.5 as the cutpoint for defining spine osteoporosis in the National Health and Nutrition Examination Survey (NHANES) 2005–2008 data (8), the prevalence of spine

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osteoporosis for older USA Caucasian women ≥50 years is 15.8% (9), which is a reasonable value because it is similar to the osteoporosis prevalence of the FN BMD definition (considering the ratio of clinical vertebral FF to hip FF is close to 1). Therefore, for Caucasian women, using the same cutpoint osteoporosis T-score (i.e., ≤–2.5) to define both FN and spine osteoporosis is justifiable, although it may not be ideal. *Figure 2* shows that, if lumbar spine T-score ≤–2.5 is taken as the cutpoint for defining osteoporosis, in addition to USA Caucasians and blacks (8,9), the data from Canada (10), Australia (11), Southern Italy (12), and Sweden (13) all demonstrate that FN BMD-classified osteoporosis (FN osteoporosis) prevalence and spine BMD-classified osteoporosis (spine osteoporosis) prevalence are similar. Löfman *et al.* (13) studied women aged 70 years and reported that FN osteoporosis prevalence and spine osteoporosis prevalence were 36% and 32%, respectively. Mautalen *et al.* (14) reported higher spine osteoporosis prevalence for the 'younger' group of their study participants and higher FN osteoporosis prevalence for the 'older' group of their study participants, consistent with the pattern that the clinical vertebral FF to hip FF ratio is higher than 1 prior to the age of 70 years and lower than 1 after the age of 70 years.

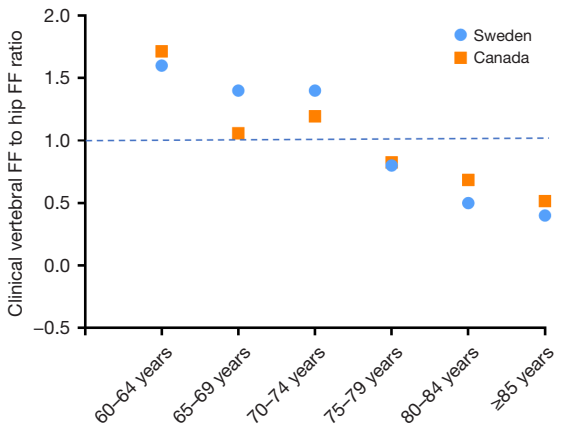

Figure 1 The clinical vertebral FF to hip FF ratio at different age groups. Data from Sweden and Canada women (6,7). FF, fragility fracture.

The FF prevalence of older Chinese women is slightly less than half that of Caucasians (9,15). This is the case for hip FF, radiographic vertebral FF (*Figure 3*) (16), clinical vertebral FF (*Figure 4*) (17,18), and many other FF sites (9,15). Since the prevalences of vertebral FF and hip FF of older Chinese women are both slightly less than half of those of Caucasians, the clinical vertebral FF to hip FF ratio is also likely to be around 1 at the age of 70 for Chinese women (i.e., the same as for Caucasians), and this is demonstrated in *Figure 4*. Moreover, in a Korean study, Lim *et al.* (19) analysed female participants from the National Health Insurance Service senior cohort (mean age: approximately 68 years), and reported clinical vertebral FF and hip FF to be 10.7% and 9.6%, respectively (derived from *Tab. 3* in reference 19). In a Japanese study of 1,342 postmenopausal women aged 50 years or more with a median follow-up of 15.2 years, Kamiya *et al.* (20) recorded 38 and 35 cases of clinical vertebral FF and hip

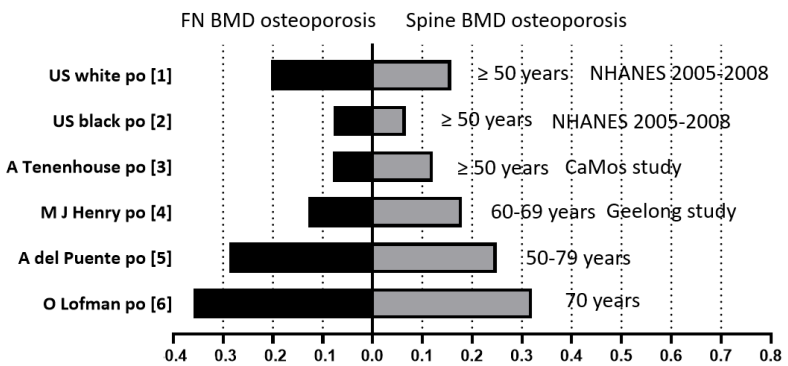

Figure 2 Graphic presentation of the ratios of areal DXA FN BMD-classified osteoporosis (FN osteoporosis) prevalence to spine BMD-classified osteoporosis (spine osteoporosis) prevalence, Caucasian and US blacks women results. X-axis: prevalence, with 0.1 denoting a prevalence of 10%. Data include US Caucasians [1], US blacks [2], Canadian [3], Australian [4], Southern Italians [5], and Swedish [6] (8-13). po: community population data. FN, femoral neck; BMD, bone mineral density; NHANES, National Health and Nutrition Examination Survey; DXA, dual-energy X-ray absorptiometry.

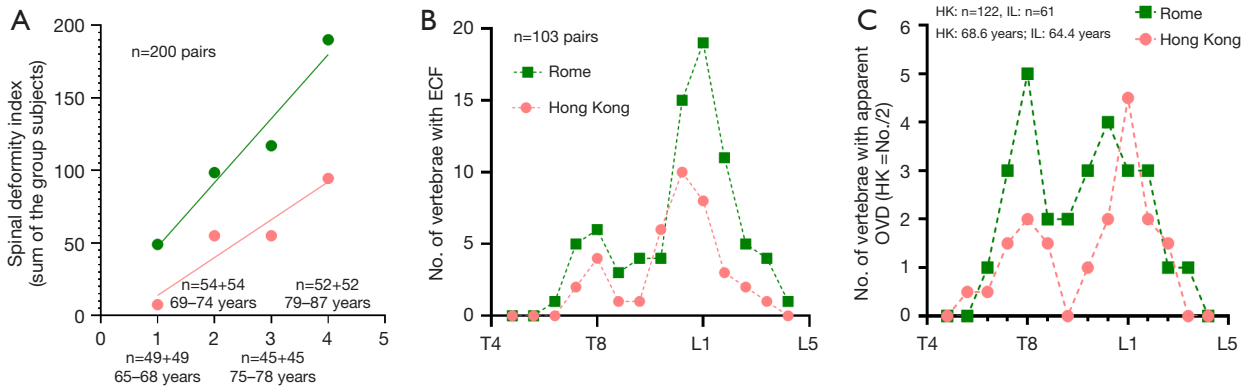

Figure 3 Older Chinese women have a much lower radiographic osteoporotic vertebral fracture prevalence than that of Italian older women. (A) Total spinal deformity index score of four different age groups of Chinese women and Italian women (population-based and age-matched data). The spinal deformity index was calculated with each vertebra assigned a score of 0, 0.5, 1, 1.5, 2, 2.5, and 3 for no ROVD or ROVDs of <20%, 20~25%, ≥25%~1/3, ≥1/3~40%, ≥40%~2/3, and ≥2/3 vertebral height loss, respectively. The spinal deformity index for each subject was calculated by summing the scores of all vertebrae from T4 to L5. The red points indicate Hong Kong subjects, and the green points indicate Italian subjects. Lines denote the linear fit of the four values of the total spinal deformity index for the four age groups, with the slope being steeper for the Italian than for the Chinese data. N=49+49 means there are 49 Chinese subjects and 49 Italian subjects in this age group. (B) A comparison of the distribution of ECF sign positive ROVD among different vertebral levels (103 pairs of age-matched Chinese and Italian older women, population-based data, mean age: 72.4 years). The data in (B) is in addition to the data in (A). (C) A comparison of the distribution of apparent ROVD (i.e., with ≥20% vertebral height loss) among different vertebral levels. There were 122 population-based Chinese subjects and 61 Italian back pain patients (ROVD number for Chinese data was divided by 2 for presentation). X-axis in (B,C): vertebral level of the spine. Data are from Wang *et al.* Arch Osteoporos 2021;16:174, and Wang *et al.*, Arch Osteoporos 2022;17:13. ECF, endplate end/or cortex fracture; HK, Hong Kong; IL, Italian; ROVD/OVD, radiological osteoporotic vertebral deformity (equivalent to radiological vertebral fracture).

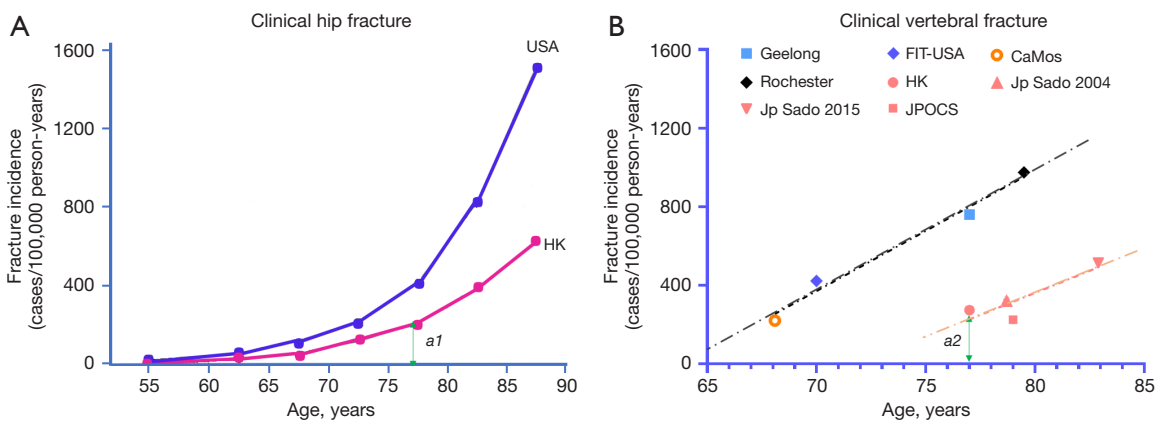

Figure 4 The clinical vertebral FF to hip FF ratio is around 1 at the age of 77 years for Chinese women. In this graph, the values of *a1* and *a2* at age 77 years are similar. (A) Age-specific hip FF incidence among Hong Kong and USA older women according to the study of Ho *et al.* (Am J Public Health 1993;83:694-7). (B) Clinical vertebral FF incidence of older Asian women and Caucasian women. Data are from MsOS (Hong Kong) study; Sakuma *et al.*, J Bone Miner Metab 2008;26:373-8 (Japan Sado 2004), Imai *et al.*, J Bone Miner Metab 2019;37:484-90 (Japan Sado 2015); Kamiya *et al.*, Maturitas 2019;130:13-20 (JPOCS); Sanders *et al.* Osteoporos Int 1999;10:240-7 (Geelong study); Cooper *et al.* J Bone Miner Res 1992;7:221-7 (Rochester study); Fink *et al.* J Bone Miner Res 2005;20:1216-22 (FIT-USA study), and Papaioannou *et al.* Osteoporos Int 2005;16:568-78 (CaMos study). The dotted black and orange lines indicate linear fits for simplicity (ideally it should be an exponential growth fit). FF, fragility fracture.

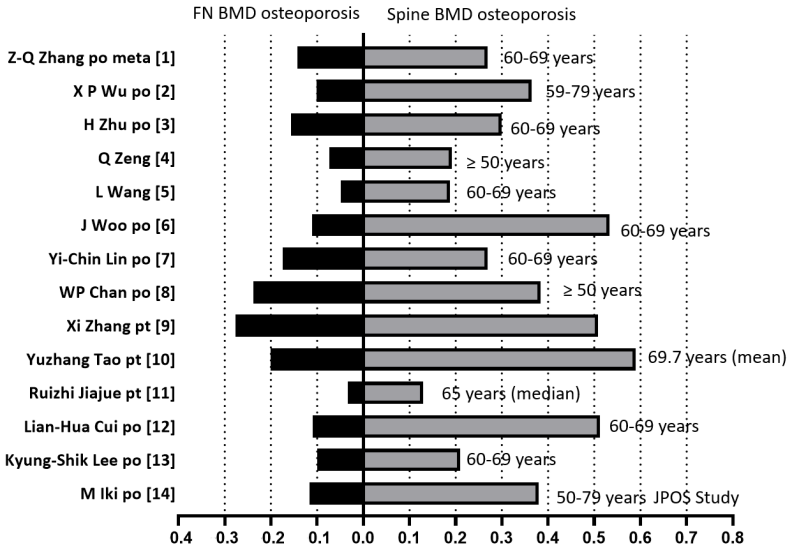

Figure 5 Graphical presentation of the ratios of areal DXA FN BMD-classified osteoporosis (FN osteoporosis) prevalence to spine BMD-classified osteoporosis (spine osteoporosis) prevalence, East Asia women results. Data from references (21-34). X-axis: prevalence, with 0.1 denoting a prevalence of 10%. [1]: meta-analysis results; [2]: Hologic device with local BMD reference; [3]: Hologic or GE Lunar devices, with local BMD reference; [4]: GE Lunar device with local BMD reference; [5]: Hologic or GE Lunar devices, with local BMD reference; [6]: Hologic device and its BMD reference; [7]: GE Lunar device with local BMD reference; [8]: Norland device with local BMD reference; [9]: Hologic device and its BMD reference; [10]: Hologic device and its BMD reference (specified for Caucasians); [11]: Lunar DPX or Norland devices and instrument BMD references; [12]: GE Lunar device with local BMD reference; [13]: Hologic device with local BMD reference; [14]: Hologic device with local BMD reference. [9]: rheumatic patients; [10]: total knee arthroplasty patients; [11]: type 2 diabetes mellitus patients. The prevalence ratio of spine osteoporosis to FN osteoporosis is: 1.89 [1], 3.6 [2], 1.91 [3], 2.64 [4], 3.84 [5], 4.8 [6], 1.54 [7], 1.61 [8], 1.84 [9], 3.0 [10], 3.94 [11], 4.66 [12], 2.1 [13], 3.28 [14], respectively. po: community population data; pt: patient data. FN, femoral neck; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry.

FF respectively. We anticipate that the dual-energy X-ray absorptiometry (DXA) based prevalence of FN osteoporosis in Chinese women will be approximately half of that of Caucasians, and that the prevalence of FN osteoporosis and spine osteoporosis will be similar in Chinese women. However, the reported data show a quite different picture. *Figure 5* shows one result from a meta-analysis of different Chinese female populations, four population-based studies from mainland China, two population-based studies from Taiwan and two population-based studies from Korea, and one each from Hong Kong and Japan (21-34). Except for the meta-analysis result, all other results were randomly selected from the literature. Overall, population-based studies from China, Korea, and Japan tend to report an FN osteoporosis prevalence of >8%, which is more than half of older Caucasian women's rate. Moreover, for all studies in *Figure 5*, the prevalence of spine osteoporosis was substantially higher than that of FN osteoporosis, with spine osteoporosis prevalence exceeding what would be expected from the variation of the clinical vertebral FF to hip FF ratio across different age bands (5-7,9-14,19,20,35,36).

Based on statistical modeling, we recently proposed that the cutpoint T-score for defining FN osteoporosis should be revised from ≤–2.5 to ≤–2.75 for Hong Kong older women when a local BMD reference range is being applied (9). This lowers the prevalence of FN osteoporosis in women ≥60 years from 14.7% to 10%. More notably, if we use the Caucasian cutpoint T-score of ≤–2.5 to define spine osteoporosis, the prevalence of spine osteoporosis for Hong Kong women ≥60 years is as high as 34.8%, which is unreasonable (also see *Figure 2* results for Caucasians). We also proposed that (9) the cutpoint T-score for defining spine osteoporosis should be revised from –2.5 to –3.74 in order to arrive at a prevalence of spine osteoporosis of 10% for Hong Kong women ≥60 years old using the local BMD reference of Lynn *et al.* (37). In an empirical study on women with radiographic vertebral FF, we recently demonstrated that, at the mean age of 73.5 years and

considering vertebral FF status, an FN T-score of –2.56 for Italian Caucasians is equivalent to –2.61 for Hong Kong Chinese, while a lumbar spine T-score of –2.7 for Italian Caucasians is equivalent to –3.54 for Hong Kong Chinese [n=310 Chinese and Italian pairs (38)]. For the 512 Chinese cases [mean age: 74.0 years, from the MsOS (Hong Kong) study] analysed in that study, 20.5% of the cases had FN osteoporosis, while 41.0% had spine osteoporosis when the conventional cutpoint T-score of –2.5 was used (38).

In conclusion, while a cutpoint T-score ≤–2.5 for defining spine osteoporosis is justified for Caucasian women, for Chinese women the same cutpoint T-score much inflates the estimated prevalence of spine osteoporosis. Despite DXA being an imperfect method for measuring bone strength, in addition to the use of a local BMD reference database, an adjusted cutpoint T-score for defining osteoporosis among elderly Chinese women should be applied, particularly for spine BMD measurements (9,38). Moreover, although this article presents female data, our earlier analysis showed a similarly inflated prevalence of spine osteoporosis in older Chinese men if the cutpoint T-score ≤–2.5 is used (9). We expect that the principles presented here may also apply to osteoporosis estimation in other East Asian populations. For example, it has been suggested that older Korean women and Japanese women have FF risk profiles similar to those of older Chinese women (*Figure 4*) (5,39-41).

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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