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META-ANALYSIS

The association between metabolic syndrome and bone mineral density: a meta-analysis

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Abstract Previous researches demonstrate uncertainty about the effect of metabolic syndrome (MS) on bone. We performed a meta-analysis to investigate the association of MS with bone mineral density (BMD) of spine and femoral neck (FN). In this meta-analysis, searches of Medline, Embase, Cochrane Library, Chinese biological medical database and China national knowledge infrastructure were undertaken to identify studies in humans of the association between MS and BMD. Random effects model was used for this meta-analysis. The results of our research were reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A total of 11 studies (including an outlier study) with 13,122 subjects were included in our research. We detected a significant overall association of MS with increased BMD of spine (weighted mean difference, WMD = 0.027, 95 % confidence interval, CI [0.011, 0.042]) and no significant overall association of MS with BMD of FN (WMD = 0.008, CI [−0.011, 0.026]). Subgroup analyses indicated significant association between MS and increased BMD of spine in subjects whose BMD was measured by dual-energy X-ray absorptiometry (DXA) scanner manufactured by Hologic Inc., subjects diagnosed by International Diabetes Federation criteria and subjects diagnosed by National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) criteria. And significant association between MS and increased BMD of FN in Caucasian subjects, subjects whose BMD was measured by DXA scanner manufactured by Hologic Inc. and subjects diagnosed by NCEP-ATP III criteria was also found. Our meta-analysis suggests that MS has no clear influence on BMD, or its influence maybe beneficial.

Keywords Metabolic syndrome · Bone mineral density · Meta-analysis · Osteoporosis

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Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength that predisposes affected persons to an increased risk of fracture [1]. Traditionally, the definition of osteoporosis is based on bone mineral density (BMD) measurements at the spine and proximal femur [2]. It is an important public health problem worldwide due to its high morbidity and mortality and its significant economic costs [3, 4]. The economic burden of osteoporosis is likely to increase in the future due to increased life expectancy and a growing population of elderly people with a high risk of fractures.

Metabolic syndrome (MS) is characterized by abdominal obesity, insulin resistance, hypertension, and dyslipidemia [5] (i.e., elevated levels of triglycerides and low levels of high-density lipoprotein cholesterol [HDL-C]). The dominant underlying risk factors for this syndrome appear to be abdominal obesity and insulin resistance. There are several similar clusters of criteria for diagnosing MS, such as International Diabetes Federation (IDF) criteria, National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) criteria and American

Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) criteria. MS is associated with an increased risk for developing cardiovascular diseases and diabetes mellitus [6, 7]. Furthermore, coexistence of the components of MS increases the cardiovascular risk more than the sum of the influence of individual component. However, they may show different associations with bone metabolism.

The components of MS may have a protective or a negative effect on bone. For instance, obesity may lead to increased BMD because it is associated with higher 17β-estradiol level and higher mechanical load, which may protect bone [8, 9]. However, visceral fat accumulation is associated with higher levels of pro-inflammatory cytokines, which may up-regulate receptor activators of nuclear factor-κB ligand, leading to increased bone resorption and decreased BMD [10–12]. The effects of other components of MS (i.e., blood pressure, serum concentrations of glucose, triglyceride and HDL-C) on BMD are also contradictory. Moreover, the association between MS and BMD may be influenced by ethnic or other factors. Thus, in some studies, the combined effect of the MS risk factors on bone health has not yet been consistent.

We therefore undertook a meta-analysis between MS and BMD, as a measure of osteoporosis, based on available studies.

Subjects, materials and methods

Search strategy and inclusion criteria

We systematically searched Medline, Embase and Cochrane Library for studies written in English and Chinese biological medical database and China national knowledge infrastructure for studies written in Chinese (from their commencements to Jan 2012). The search used the following terms: "metabolic syndrome", "MS", "bone", "bone mineral density", "BMD", "osteoporosis", "OP" and "osteopenia". The following two sites of BMD were included in this meta-analysis: spine and femoral neck (FN).

Studies in humans of the association between MS and BMD, regardless of sample size, were included if they met the following criteria: (1) the study was written in English or Chinese; (2) data were reported on at least one of the two sites (spine and FN) of BMD; (3) BMD was measured by dual-energy X-ray absorptiometry (DXA) and expressed by g/cm^2; (4) we only included studies in which mean BMD and standard deviations (SDs) or standard errors (SEs) were available; (5) subjects were adults who were at least 18 years old. The excluded studies included reviews, editorials, comments, letters, and abstracts.

Data extraction

Two investigators independently reviewed the articles and selected eligible studies according to the inclusion criteria for eligible studies. Irrelevant studies were excluded. For studies with same population resources or overlapping datasets, the most complete one was included. Study details and data were extracted independently to a standardized electronic form by two investigators, and discrepancies were adjudicated by a third reviewer until consensus was achieved on every item. The following information was extracted from each study: last name of first author, year of publication, country, subject population, definition of MS, mean BMD and SDs (or SEs) of subjects with or without MS. We used unadjusted BMD in our meta-analysis.

Statistical analysis

For this meta-analysis, all data should be given as mean and SDs. In those studies where values of SEs were originally reported, the values of SDs were calculated. When information was reported for more than one subpopulation (for example, male subjects or female subjects) in one study, each subpopulation was treated as a separate comparison in our meta-analysis. BMD in the two sites (spine and FN) were continuous outcomes presented on the same scale (g/cm^2), so we used a WMD with 95 % confidence intervals (CIs) calculated using the final follow-up P values provided for the MS (+) and MS (−) groups to analyze the strength of the association between MS and BMD. All data were initially analyzed with a fixed effects model. If heterogeneity was found, the analysis should be redone using a random effects model. A P value of 0.05 was considered statistically significant.

Heterogeneity of the effect across studies was assessed by Q statistics, which is distributed as χ^2 statistics. I^2 statistics were provided to quantify the percentage of total variation across studies that was attributable to heterogeneity rather than to chance. An I^2 value >50 % represented substantial variability. In the presence of heterogeneity, sensitivity analyses were performed to indentify the outlier studies. The influence of outliers was also assessed to evaluate the impact of their removal. Moreover, there might be effect modification caused by study-level characteristics including gender, ethnicity, manufacturer of DXA scanner and MS definition. These were identified by performing a meta-regression for each study-level variable. We considered heterogeneity and meta-regression to be significant at $P < 0.10$, a conservative standard for meta-analyses. After the predefinition of each study-level variable by meta-regression, subgroup analyses were conducted. Gender subgroups were defined as male and female. Ethnic subgroups were defined as Caucasians or

Asians. Manufacturer of DXA scanner subgroups were defined as GE-Lunar and Hologic Inc. MS definition subgroups were defined as IDF criteria or NCEP-ATP III criteria, since the studies using other national criteria (AHA/NHLBI criteria and Chinese diabetes society [CDS] criteria) are too few.

We performed a visual inspection of the funnel plot for publication bias. The funnel plot should be asymmetric when there is publication bias and symmetric in the case of no publication bias. We performed Egger and Begg tests to measure the funnel plot asymmetry using a significance level of $P < 0.05$. The trim and fill computation was used to estimate the effect of publication bias.

All statistical analyses were performed by using STATA 11.0 (Stata Corporation, College Station, TX). The results of our research were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results

Studies included in the meta-analysis

Our literature search produced 503 citations (411 written in English and 92 written in Chinese), of which we selected 21 for further review of the full text. A total of 10 studies were excluded for unavailable or incomplete data [13–22]. Finally, 11 unique studies were available for this meta-analysis [23–33]. Of these, 10 studies (included 14 comparisons) and 7 studies (included 11 comparisons) separately presented data on BMD of spine and FN. Table 1 summarizes the characteristics of the included studies.

In all eligible studies, there were five studies separately providing the information on more than one subpopulation. Each subpopulation was treated as a separate comparison. A total of 13,122 subjects were included in this meta-analysis. Among them, 2,779 were with MS, and 10,343 were without MS.

Association between MS and BMD of spine

We initially performed the meta-analysis on all 10 studies (including 14 comparisons) with a fixed effects model. For the presence of significant heterogeneity ($I^2 = 90.8$ %), the analysis was redone using a random effects model. The results did not suggest the significant association between MS and BMD of spine (weighted mean difference, WMD = 0.021, 95 % CI [−0.003, 0.044], $P = 0.081$; $I^2 = 90.8$ %, $P < 0.001$ for Q test). Since the value of I^2 was very high, the results above were unavailable.

Thus, there might be outlier studies which should be identified by sensitivity analyses and then be omitted. Sensitivity analyses showed that there was an outlier study (study ID: Hwang and Choi [27]). When the outlier study was omitted, 9 studies (including 13 comparisons) were included in the meta-analysis. The heterogeneity was decreased and the results suggested the significant association between the MS and increased BMD of spine (WMD = 0.027, 95 % CI [0.011, 0.042], $P = 0.001$; $I^2 = 74.3$ %, $P < 0.001$ for Q test) (Fig. 1).

Table 1 Characteristics of included studies on the association between MS and BMD

References	Countries	Study subjects	MS definitions	BMD sites	DXA scanner manufacturers
Pasco et al. [61]	Australia	641 Men aged 50–93	IDF	Spine and FN	GE-Lunar
Jeon et al. [23]	Korea	2165 Women aged ≥45	AHA/NHLBI	Spine and FN	GE-Lunar
Szulc et al. [24]	France	762 Men aged 50–85	NCEP-ATP III	Spine and FN	Hologic Inc.
Park et al. [25]	Korea	399 Postmenopausal women aged 59.4 ± 6.7	NCEP-ATP III	Spine and FN	GE-Lunar
Muhlen et al. [26]	United States	417 Men and 671 postmenopausal women aged 38–97	NCEP-ATP III	Spine and FN	Hologic Inc.
Hwang and Choi [27]	Korea	2475 Women aged 21–94	NCEP-ATP III	Spine	Hologic Inc.
Boyanov et al. [28]	Bulgaria	172 Men aged 51.9 ± 9.0	IDF	Spine	Hologic Inc.
Hernandez et al. [29]	Spain	1508 Men and women aged ≥50	NCEP-ATP III	Spine and FN	Hologic Inc.
Zhang et al. [32, 33]	China	247 Men (aged 53.71 ± 10.36) and 227 women (aged 58.75 ± 10.93)	CDS	Spine	GE-Lunar
Yaturu et al. [30]	United States	550 Men aged 50–76	NCEP-ATP III	Spine	GE-Lunar
Kim et al. [31][a]	Korea	1108 Postmenopausal women and 1780 men aged >40	IDF	FN	GE-Lunar

[a] In this study, MS was defined by IDF and AHA/NHLBI respectively. We choose the former to avoid overlapping

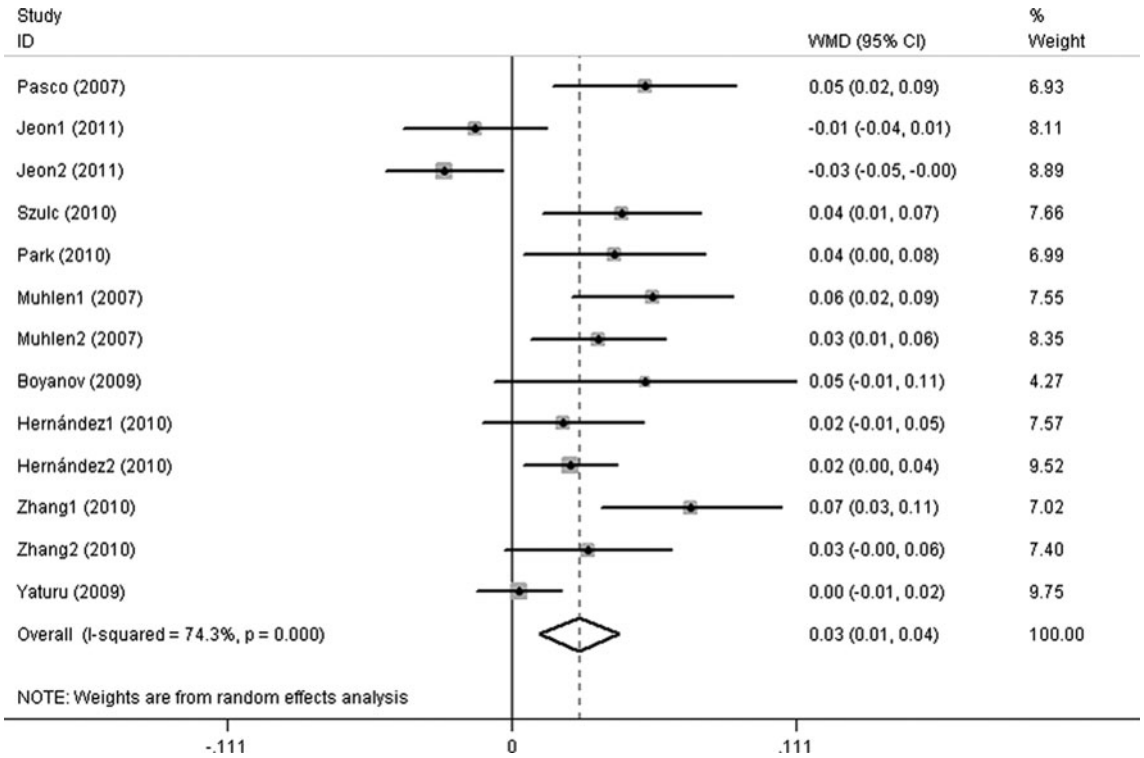

Fig. 1 Forest plot of the association between MS and BMD of spine using a random effects model

Meta-regression did not show a significant difference in effect estimates among studies focus on male subjects versus those focus on female subjects (meta-regression $P = 0.425$). Likewise, meta-regression results indicated a lack of effect measure modification by ethnicity ($P = 0.118$). However, meta-regression results indicated significant effect measure modification by Manufacturer of DXA scanner ($P = 0.053$) and MS definition ($P = 0.087$).

We therefore carried subgroup analyses to examine whether the results for the association between MS and BMD of spine were different with the Manufacturer of DXA scanner and MS definition. Significant association between the MS and increased BMD of spine was detected in subjects whose BMD was measured by DXA scanner manufactured by Hologic Inc. (WMD = 0.033, 95 % CI [0.021, 0.044], $P < 0.001$, $I^2 = 0.0$ %, $P = 0.489$ for Q test), subjects diagnosed by IDF criteria (WMD = 0.052, 95 % CI [0.021, 0.083], $P = 0.001$, $I^2 = 0.0$ %, $P = 1.000$ for Q test) and subjects diagnosed by NCEP-ATP III criteria (WMD = 0.028, 95 % CI [0.014, 0.042], $P < 0.001$, $I^2 = 52.2$ %, $P = 0.051$ for Q test). The remaining results from these subgroup analyses were not significant ($P > 0.05$).

Association between MS and BMD of FN

Similarly, we performed the meta-analysis on all 7 studies (including 11 comparisons) with a random effects model (Fig. 2), and the results did not suggest the significant association between MS and BMD of FN (WMD = 0.008, 95 % CI [−0.011, 0.026], $P = 0.427$, $I^2 = 86.0$ %, $P < 0.001$ for Q test).

Sensitivity analyses showed that there was no outlier study. Meta-regression did not show a significant difference in effect estimates among studies focus on male subjects versus those focus on female subjects (meta-regression $P = 0.431$). However, meta-regression results indicated significant effect measure modification by ethnicity ($P = 0.014$), Manufacturer of DXA scanner ($P = 0.027$) and MS definition ($P = 0.009$).

We therefore carried subgroup analyses to examine whether the results for the association between MS and BMD of spine were different with ethnicity, Manufacturer of DXA scanner and MS definition. The results suggested significant association between the MS and increased BMD of FN in Caucasian subjects (WMD = 0.029, 95 % CI [0.020, 0.038], $P < 0.001$, $I^2 = 0.0$ %, $P = 0.465$ for Q test), subjects whose BMD was measured by DXA scanner manufactured by Hologic Inc. (WMD = 0.029, 95 % CI [0.018, 0.040], $P < 0.001$, $I^2 = 12.9$ %, $P = 0.332$ for Q test) and subjects diagnosed by NCEP-ATP III criteria (WMD = 0.029, 95 % CI [0.020, 0.038], $P < 0.001$, $I^2 = 0.0$ %, $P = 0.467$ for Q test). The remaining results from these subgroup analyses were not significant ($P > 0.05$).

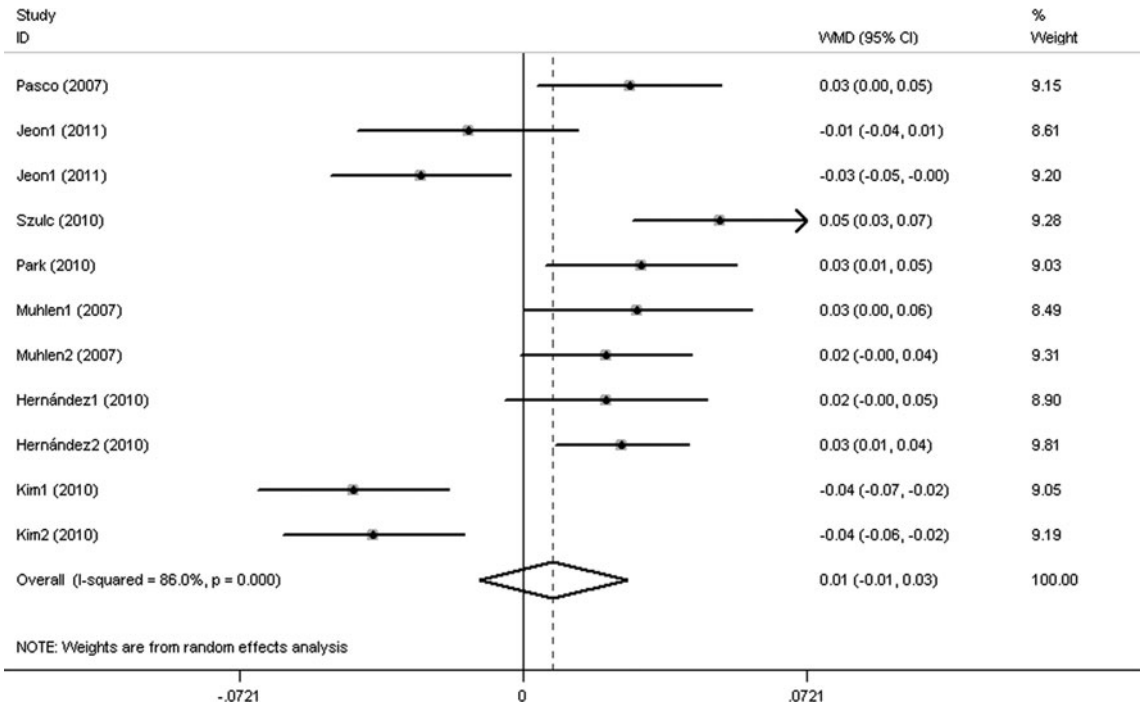

Fig. 2 Forest plot of the association between MS and BMD of FN using a random effects model

Heterogeneity and publication bias

Significant heterogeneity was separately observed among the available studies on BMD of spine and FN. To detect the source of heterogeneity, we performed meta-regression and subgroup analyses stratified by the characteristics of the subjects. Significant heterogeneity was removed or decreased in some subgroups, but still existed in other subgroups (Table 2).

The number of studies included in the analysis was relatively small, so it was difficult to correlate the funnel plot. For the 9 studies (with an outlier study excluded) focus on BMD of spine, both Egger's regression ($P = 0.041$) and Begg's methods ($P = 0.044$) showed publication bias. Trim and fill analysis results showed five studies might have been missing. When they were added to the meta-analysis, a WMD value was 0.010 (95 % CI [0.003, 0.017]), which suggested the significant association between the MS and increased BMD of spine either. For the seven studies focus on BMD of FN, both Egger's regression ($P = 0.523$) and Begg's methods ($P = 0.436$) did not indicate publication bias.

Discussion

In our meta-analysis, we used unadjusted BMD. Although in general, the adjusted BMD were more accurate and

Table 2 Heterogeneity in subgroups

Subgroups	BMD of spine			BMD of FN		
	I^2 (%)	χ^2	P	I^2	χ^2	P
Ethnicity						
Caucasian	–	–	–	0.0	4.62	0.465
Asian	–	–	–	82.2	22.52	0.000
Manufacturer of DXA scanner						
GE-Lunar	82.1	33.60	0.000	85.7	34.92	0.000
Hologic Inc.	0.0	4.43	0.489	12.9	4.59	0.332
MS definition						
IDF	0.0	0.00	1.000	90.6	21.37	0.000
NCEP-ATP III	52.2	12.56	0.051	0.0	4.60	0.467

deeper considered, it was not appropriate to our research. In the studies in which BMD were adjusted, one of the adjusting factors was BMI or body weight. Such an adjustment distorted the clinical profile of MS, which by definition included high body weight, waist perimeter or BMI. When adjusting for these, the clinical sense of MS just disappeared, or was at least essentially modified. Therefore, we choose the unadjusted BMD for our meta-analysis.

Through sensitivity analyses, we detected an outlier study when we performed the meta-analysis on the association of MS with BMD of spine. In this study, mean vertebral BMD was significantly lower in women with MS than women without. The subjects of this outlier study were aged 21–94, but the subjects of the other nine studies were mainly middle-aged or older people. This might be the main reason for the detection of the outlier study. Therefore, we could assume that the association of MS with BMD of spine might be different in young and old people.

A significant overall association of MS with increased BMD of spine and no significant overall association of MS with BMD of FN was detected in our meta-analysis. Since MS is a cluster of conditions interacting with each other, the mechanism behind the effects of MS on BMD is complicated and has not yet been investigated in detail. The associations between individual components of the MS and BMD have been extensively studied, but results are inconclusive. (1) Obesity: abdominal obesity is not only a key component of MS but also a cause of MS inducing insulin resistance. High BMI is considered to be a protecting factor against excessive bone loss in several studies [34–37]. In addition, Edelstein and Barrett-Connor [38] reported a positive association of central obesity and higher BMD levels at all sites in both genders. However, some other studies indicated that central obesity was significantly associated with low bone mass [39–42]. (2) Impaired glucose tolerance: in several different studies, impaired glucose tolerance was associated with lower, higher, or similar BMD compared with the control individuals [17, 43–46]. (3) Hypertension: some studies reported that hypertension is related with low bone mass due to the changes of serum intact PTH concentration or urinary calcium excretion [47, 48]. But the results are inconsistent. Hanley et al. [49] found an independent association of hypertension with higher BMD for both genders. Mussolino and Gillum [50] found no significant association between blood pressure and BMD at any bone site. (4) Triglyceride: Edelstein and Barrett-Connor [38] found that triglyceride positively correlates with BMD. Moreover, experimental data suggest that apolar lipids, including TG, form a layer between collagen fibers and mineral crystals. So, TG may mediate the interaction between protein matrix and bone mineral and contribute to the improvement of qualitative properties of bone [51]. But Kim et al. [31] found that triglyceride levels were negatively associated with BMD of FN in postmenopausal women. (5) HDL-C: Adami et al. [52] found that hip BMD was negatively associated with HDL-C in both genders. But another two studies showed that HDL-C positively correlates with BMD in the lumbar spine in postmenopausal women [53, 54]. Therefore, the combined effect of the MS components on BMD could be positive or insignificant.

Significant heterogeneity was found in our meta-analysis. Several study-level variables leading to heterogeneity were defined by meta-regression and subgroup analyses, such as ethnicity, DXA scanner manufacturer and MS definition. First, we detected positively association between MS and BMD of FN in Caucasian subjects rather than Asian subjects. Visceral adiposity has been linked to reduced bone mass, and Asians have more visceral adiposity than do Caucasians, despite a similar rate of general obesity. Therefore, Asians with MS may be more influenced by visceral adiposity [55, 56]. Second, we detected positively association between MS and BMD of spine and FN in the subjects whose BMD was measured by DXA scanner manufactured by Hologic Inc. rather than GE-Lunar. Absolute values of BMD, using DXA, might differ between instruments from different manufacturers. Previous study performed a comparison of longitudinal measurements in the spine and proximal femur using Lunar and Hologic instruments [57]. Despite the significant correlations, the agreement between the two densitometers was not high and there might be significant errors in individual subjects if one uses measurements from one densitometer to predict the change in BMD using the scanner of the other manufacturer. Third, we detected positively association between MS and BMD of FN in the subjects diagnosed by NCEP-ATP III criteria rather than IDF criteria. According to NCEP-ATP III or IDF criteria, participants were classified as having MS when any three or more of the following items were present: (1) abdominal obesity, (2) high triglycerides, (3) low HDL-C levels, (4) high fasting glucose or (5) high blood pressure. Although each criterion was similar between the two clusters of criteria, there was still obvious difference. For instance, abdominal obesity was a necessary criterion in IDF criteria rather than NCEP-ATP III criteria.

Heterogeneity was removed or decreased in some subgroups but still existed in other subgroups. Thus, in addition to ethnicity, Manufacturer of DXA scanner and MS definition, there might be other factors leading to heterogeneity, such as different sample size. Moreover, previous study indicated that gender might influence the association between MS and BMD [58]. It could be hypothesized that, because of the partially different type of fat deposition in

women and in men, the conditions of mechanical effect, adipocyte estrogen synthesis and chronic low-grade inflammation may be also different in genders. But gender was not defined as an variable leading to heterogeneity by meta-regression in our research.

For the studies focus on BMD of spine, Egger's regression and Begg's methods showed publication bias. Usually, publication bias appeared for only significant results were published. But in our research, that might not be the main reason because no significant effect was present in some studies included in our meta-analysis. In the process of our literature search, we retrieved some abstracts (written in English) reporting the association between MS and BMD, but the full texts of the papers were published in other languages (Japanese, Russian, et al.). We could not get the full papers, which might lead to publication bias. Publication bias was adjusted by trim and fill analysis in our research, and the results of meta-analysis were similar with those before the adjustment. Thus, the publication bias had no great impact on our meta-analysis. For the studies focus on BMD of FN, both Egger's regression and Begg's methods did not indicate publication bias.

Considered together, these studies seem to indicate that MS either has no clear influence on BMD, or its influence maybe beneficial.

The present study has some limitations that should be considered. First, several sites for BMD measurement (i.e. hip, spine and FN) have been researched. We only included BMD of spine and FN in this meta-analysis because these two sites were most extensively studied. Second, since we used unadjusted BMD in our meta-analysis, the results might be influenced by confounders. For example, body size might influence BMD measurements. So it was seemingly necessary to adjust BMD by BMI. However, as we all know, BMI was an element of MS, and, hence, adjusting for it implies an essential modification in the situation studied, which would be different from MS itself. Therefore, despite the presence of confounders, we had to choose the unadjusted BMD. Third, the number of studies included in our meta-analysis was limited. Thus, when we performed subgroup analyses, the statistical power could be inadequate. Fourth, we only included the studies published in English or Chinese because it was very difficult to get the full papers published in various languages, which might affect our final conclusions. Fifth, osteoporosis was due to alteration of both bone density and quality, leading to increased risk of fragility fractures. But we only evaluated the effects of MS on BMD, which was one-sided. For example, BMD of the diabetes might not truly reflect bone biomechanical competence, and their fracture risk might be increased despite normal or increased BMD [59]. Furthermore, the mechanism of bone metabolism differed in diabetes and non-diabetes. For instance, Hamada et al. [60] found that receptor for advanced glycation end products (RAGE) played a crucial role in bone metabolism under physiological conditions, but AGEs-RAGE interaction may not be involved in the bone metabolism in diabetes. Thus, we should pay more attention to bone quality than bone mass of the patients with MS if they had diabetes.

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Conflict of interest None of the authors has any conflicts of interest to declare.

References

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, Osteoporosis prevention, diagnosis, and therapy. JAMA **285**(6), 785–795 (2001)
2. Writing Group for the ISCD Position Development Conference, Diagnosis of osteoporosis in men, premenopausal women, and children. J. Clin. Densitom. **7**(1), 17–26 (2004)
3. J.Y. Reginster, P. Gillet, W. Ben Sedrine, G. Brands, O. Ethgen, C. de Froidmont, C. Gosset, Direct costs of hip fractures in patients over 60 years of age in Belgium. Pharmacoeconomics **15**(5), 507–514 (1999)
4. C. Gazzaruso, An increased risk for fractures: another cause of frailty in HIV-infected subjects. Endocrine (2012). doi:10.1007/s12020-012-9640-0
5. M.A. Cornier, D. Dabelea, T.L. Hernandez, R.C. Lindstrom, A.J. Steig, N.R. Stob, R.E. Van Pelt, H. Wang, R.H. Eckel, The metabolic syndrome. Endocr. Rev. **29**(7), 777–822 (2008). doi:10.1210/er.2008-0024
6. A.S. Gami, B.J. Witt, D.E. Howard, P.J. Erwin, L.A. Gami, V.K. Somers, V.M. Montori, Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J. Am. Coll. Cardiol. **49**(4), 403–414 (2007). doi:10.1016/j.jacc.2006.09.032
7. E.S. Ford, C. Li, N. Sattar, Metabolic syndrome and incident diabetes: current state of the evidence. Diabetes Care **31**(9), 1898–1904 (2008). doi:10.2337/dc08-0423
8. L.R. Nelson, S.E. Bulun, Estrogen production and action. J. Am. Acad. Dermatol. **45**(3 Suppl), S116–S124 (2001)
9. H. Ohta, T. Ikeda, T. Masuzawa, K. Makita, Y. Suda, S. Nozawa, Differences in axial bone mineral density, serum levels of sex steroids, and bone metabolism between postmenopausal and age- and body size-matched premenopausal subjects. Bone **14**(2), 111–116 (1993)
10. L.C. Hofbauer, M. Schoppet, Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. JAMA **292**(4), 490–495 (2004). doi:10.1001/jama.292.4.490
11. B.J. Smith, M.R. Lerner, S.Y. Bu, E.A. Lucas, J.S. Hanas, S.A. Lightfoot, R.G. Postier, M.S. Bronze, D.J. Brackett, Systemic bone loss and induction of coronary vessel disease in a rat model of chronic inflammation. Bone **38**(3), 378–386 (2006). doi:10.1016/j.bone.2005.09.008
12. R.M. Campos, A. de Piano, P.L. da Silva, J. Carnier, P.L. Sanches, F.C. Corgosinho, D.C. Masquio, M. Lazaretti-Castro, L.M. Oyama, C.M. Nascimento, L. Tock, M.T. de Mello, S. Tufik, A.R. Damaso, The role of pro/anti-inflammatory adipokines on

bone metabolism in NAFLD obese adolescents: effects of long-term interdisciplinary therapy. Endocrine (2012). doi:10.1007/s12020-012-9613-3
13. S. Cvijetic, M. Pavlovic, D. Pasalic, S. Dodig, Ultrasound bone measurement in an older population with metabolic syndrome. Aging Clin Exp Res **23**(1), 29–34 (2011)
14. D.N. Binici, N. Gunes, Risk factors leading to reduced bone mineral density in hemodialysis patients with metabolic syndrome. Ren. Fail. **32**(4), 469–474 (2010). doi:10.3109/08860221003675260
15. M. Kinjo, S. Setoguchi, D.H. Solomon, Bone mineral density in adults with the metabolic syndrome: analysis in a population-based U.S. sample. J. Clin. Endocrinol. Metab. **92**(11), 4161–4164 (2007). doi:10.1210/jc.2007-0757
16. Y.H. Tseng, K.C. Huang, M.L. Liu, W.T. Shu, W.H. Sheu, Association between metabolic syndrome (MS) and bone mineral loss: a cross-sectional study in Puli Township in Taiwan. Arch. Gerontol. Geriatr. **49**(Suppl 2), S37–S40 (2009). doi:10.1016/S0167-4943(09)70011-1
17. T. Yamaguchi, I. Kanazawa, M. Yamamoto, S. Kurioka, M. Yamauchi, S. Yano, T. Sugimoto, Associations between components of the metabolic syndrome versus bone mineral density and vertebral fractures in patients with type 2 diabetes. Bone **45**(2), 174–179 (2009). doi:10.1016/j.bone.2009.05.003
18. L.A. Ahmed, H. Schirmer, G.K. Berntsen, V. Fonnebo, R.M. Joakimsen, Features of the metabolic syndrome and the risk of non-vertebral fractures: the Tromso study. Osteoporos. Int. **17**(3), 426–432 (2006). doi:10.1007/s00198-005-0003-z
19. G. Iacobellis, M. Iorio, N. Napoli, D. Cotesta, L. Zinnamosca, C. Marinelli, L. Petramala, S. Minisola, E. D'Erasmo, C. Letizia, Relation of adiponectin, visfatin and bone mineral density in patients with metabolic syndrome. J. Endocrinol. Investig. **34**(1), e12–e15 (2011). doi:10.3275/7170
20. H.T. Lee, J. Shin, Y.H. Lim, B.K. Kim, Y.T. Kim, J.U. Lee, S. Hong, S.Y. Song, S.H. Cho, The relationship between coronary artery calcification and bone mineral density in patients according to their metabolic syndrome status. Korean Circ. J. **41**(2), 76–82 (2011). doi:10.4070/kcj.2011.41.2.76
21. L.J. Lu, F. Nayeem, K.E. Anderson, J.J. Grady, M. Nagamani, Lean body mass, not estrogen or progesterone, predicts peak bone mineral density in premenopausal women. J. Nutr. **139**(2), 250–256 (2009). doi:10.3945/jn.108.098954
22. J. Lidfeldt, L. Holmdahl, G. Samsioe, C. Nerbrand, P. Nyberg, B. Schersten, C.D. Agardh, The influence of hormonal status and features of the metabolic syndrome on bone density: a population-based study of Swedish women aged 50 to 59 years. The women's health in the Lund area study. Metabolism **51**(2), 267–270 (2002)
23. Y.K. Jeon, J.G. Lee, S.S. Kim, B.H. Kim, S.J. Kim, Y.K. Kim, I.J. Kim, Association between bone mineral density and metabolic syndrome in pre- and postmenopausal women. Endocr. J. **58**(2), 87–93 (2011)
24. P. Szulc, A. Varennes, P.D. Delmas, J. Goudable, R. Chapurlat, Men with metabolic syndrome have lower bone mineral density but lower fracture risk—the MINOS study. J. Bone Miner. Res. **25**(6), 1446–1454 (2010). doi:10.1002/jbmr.13
25. K.K. Park, S.J. Kim, E.S. Moon, Association between bone mineral density and metabolic syndrome in postmenopausal Korean women. Gynecol. Obstet. Investig. **69**(3), 145–152 (2010). doi:10.1159/000264665
26. D. von Muhlen, S. Safii, S.K. Jassal, J. Svartberg, E. Barrett-Connor, Associations between the metabolic syndrome and bone health in older men and women: the Rancho Bernardo study. Osteoporos. Int. **18**(10), 1337–1344 (2007). doi:10.1007/s00198-007-0385-1
27. D.K. Hwang, H.J. Choi, The relationship between low bone mass and metabolic syndrome in Korean women. Osteoporos. Int. **21**(3), 425–431 (2010). doi:10.1007/s00198-009-0990-2
28. M. Boyanov, D. Bakalov, Z. Boneva, Bone mineral density in men with and without the metabolic syndrome. Aging Male **12**(2–3), 62–65 (2009). doi:10.1080/13685530903150812
29. J.L. Hernandez, J.M. Olmos, E. Pariente, J. Martinez, C. Valero, P. Garcia-Velasco, D. Nan, J. Llorca, J. Gonzalez-Macias, Metabolic syndrome and bone metabolism: the Camargo Cohort study. Menopause **17**(5), 955–961 (2010). doi:10.1097/gme.0b013e3181e39a15
30. S. Yaturu, S. Humphrey, C. Landry, S.K. Jain, Decreased bone mineral density in men with metabolic syndrome alone and with type 2 diabetes. Med. Sci. Monit. **15**(1), CR5–CR9 (2009)
31. H.Y. Kim, J.W. Choe, H.K. Kim, S.J. Bae, B.J. Kim, S.H. Lee, J.M. Koh, K.O. Han, H.M. Park, G.S. Kim, Negative association between metabolic syndrome and bone mineral density in Koreans, especially in men. Calcif. Tissue Int. **86**(5), 350–358 (2010). doi:10.1007/s00223-010-9347-2
32. Y.-J. Zhang, W. Zhao, H. Zhang, X.-M. Wu, L.-J. Jiang, X.-C. Song, M. Li, Effect of metabolic syndrome on bone mineral density of male patients with type 2 diabetes. TianJin Med. J. **38**(3), 230–232 (2010)
33. Y.-J. Zhang, W. Zhao, H. Zhang, J. Liu, X.-Q. Chen, S.-S. Cui, L. Zhang, Analysis of the related factors of bone mineral density in female patients with type 2 diabetes complicated metabolic syndrome. Chin. J. Prev. Control Chronic Dis. **18**(05), 481–482 (2010)
34. D.T. Felson, Y. Zhang, M.T. Hannan, J.J. Anderson, Effects of weight and body mass index on bone mineral density in men and women: the Framingham study. J. Bone Miner. Res. **8**(5), 567–573 (1993). doi:10.1002/jbmr.5650080507
35. R. Marcus, G. Greendale, B.A. Blunt, T.L. Bush, S. Sherman, R. Sherwin, H. Wahner, B. Wells, Correlates of bone mineral density in the postmenopausal estrogen/progestin interventions trial. J. Bone Miner. Res. **9**(9), 1467–1476 (1994). doi:10.1002/jbmr.5650090920
36. C. De Laet, J.A. Kanis, A. Oden, H. Johanson, O. Johnell, P. Delmas, J.A. Eisman, H. Kroger, S. Fujiwara, P. Garnero, E.V. McCloskey, D. Mellstrom, L.J. Melton III, P.J. Meunier, H.A. Pols, J. Reeve, A. Silman, A. Tenenhouse, Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporos. Int. **16**(11), 1330–1338 (2005). doi:10.1007/s00198-005-1863-y
37. J.M. Gimble, M.E. Nuttall, Bone and fat: old questions, new insights. Endocrine **23**(2–3), 183–188 (2004). doi:10.1385/ENDO:23:2-3:183
38. S.L. Edelstein, E. Barrett-Connor, Relation between body size and bone mineral density in elderly men and women. Am. J. Epidemiol. **138**(3), 160–169 (1993)
39. E.A. Jankowska, E. Rogucka, M. Medras, Are general obesity and visceral adiposity in men linked to reduced bone mineral content resulting from normal ageing? A population-based study. Andrologia **33**(6), 384–389 (2001)
40. R. Blaauw, E.C. Albertse, S. Hough, Body fat distribution as a risk factor for osteoporosis. S. Afr. Med. J. **86**(9), 1081–1084 (1996)
41. C. Torti, G. Mazziotti, P.A. Soldini, E. Foca, R. Maroldi, D. Gotti, G. Carosi, A. Giustina, High prevalence of radiological vertebral fractures in HIV-infected males. Endocrine (2011). doi:10.1007/s12020-011-9586-7
42. S.S. Moon, Y.S. Lee, S.W. Kim, Association of nonalcoholic fatty liver disease with low bone mass in postmenopausal women. Endocrine (2012). doi:10.1007/s12020-012-9639-6
43. A.H. Holmberg, P.M. Nilsson, J.A. Nilsson, K. Akesson, The association between hyperglycemia and fracture risk in middle age. A prospective, population-based study of 22,444 men and

10,902 women. J. Clin. Endocrinol. Metab. **93**(3), 815–822 (2008). doi:10.1210/jc.2007-0843
44. I. Kanazawa, T. Yamaguchi, M. Yamamoto, M. Yamauchi, S. Yano, T. Sugimoto, Combination of obesity with hyperglycemia is a risk factor for the presence of vertebral fractures in type 2 diabetic men. Calcif. Tissue Int. **83**(5), 324–331 (2008). doi:10.1007/s00223-008-9178-6
45. K. Agbaht, A. Gurlek, J. Karakaya, M. Bayraktar, Circulating adiponectin represents a biomarker of the association between adiposity and bone mineral density. Endocrine **35**(3), 371–379 (2009). doi:10.1007/s12020-009-9158-2
46. G. Mazziotti, M. Gola, A. Bianchi, T. Porcelli, A. Giampietro, V. Cimino, M. Doga, C. Gazzaruso, L. De Marinis, A. Giustina, Influence of diabetes mellitus on vertebral fractures in men with acromegaly. Endocrine **40**(1), 102–108 (2011). doi:10.1007/s12020-011-9486-x
47. D.E. Grobbee, W.H. Hackeng, J.C. Birkenhager, A. Hofman, Raised plasma intact parathyroid hormone concentrations in young people with mildly raised blood pressure. Br. Med. J. (Clin. Res. Ed.) **296**(6625), 814–816 (1988)
48. G.S. Hughes Jr, M.J. Oexmann, H.S. Margolius, S. Epstein, N.H. Bell, Normal vitamin D and mineral metabolism in essential hypertension. Am. J. Med. Sci. **296**(4), 252–259 (1988)
49. D.A. Hanley, J.P. Brown, A. Tenenhouse, W.P. Olszynski, G. Ioannidis, C. Berger, J.C. Prior, L. Pickard, T.M. Murray, T. Anastassiades, S. Kirkland, C. Joyce, L. Joseph, A. Papaioannou, S.A. Jackson, S. Poliquin, J.D. Adachi, Associations among disease conditions, bone mineral density, and prevalent vertebral deformities in men and women 50 years of age and older: cross-sectional results from the Canadian Multicentre Osteoporosis Study. J. Bone Miner. Res. **18**(4), 784–790 (2003). doi:10.1359/jbmr.2003.18.4.784
50. M.E. Mussolino, R.F. Gillum, Bone mineral density and hypertension prevalence in postmenopausal women: results from the Third National Health and Nutrition Examination Survey. Ann. Epidemiol. **16**(5), 395–399 (2006). doi:10.1016/j.annepidem.2005.06.051
51. S. Xu, J.J. Yu, Beneath the minerals, a layer of round lipid particles was identified to mediate collagen calcification in compact bone formation. Biophys. J. **91**(11), 4221–4229 (2006). doi:10.1529/biophysj.105.075804
52. S. Adami, V. Braga, M. Zamboni, D. Gatti, M. Rossini, J. Bakri, E. Battaglia, Relationship between lipids and bone mass in 2 cohorts of healthy women and men. Calcif. Tissue Int. **74**(2), 136–142 (2004). doi:10.1007/s00223-003-0050-4
53. T. Yamaguchi, T. Sugimoto, S. Yano, M. Yamauchi, H. Sowa, Q. Chen, K. Chihara, Plasma lipids and osteoporosis in postmenopausal women. Endocr. J. **49**(2), 211–217 (2002)
54. E.M. Dennison, H.E. Syddall, A. Aihie Sayer, H.J. Martin, C. Cooper, Lipid profile, obesity and bone mineral density: the Hertfordshire Cohort study. QJM **100**(5), 297–303 (2007). doi:10.1093/qjmed/hcm023
55. W.Y. Fujimoto, Overview of non-insulin-dependent diabetes mellitus (NIDDM) in different population groups. Diabet. Med. **13**(9 Suppl 6), S7–S10 (1996)
56. N. Abate, M. Chandalia, The impact of ethnicity on type 2 diabetes. J. Diabetes Complicat. **17**(1), 39–58 (2003)
57. N.A. Pocock, K.A. Noakes, M. Griffiths, N. Bhalerao, P.N. Sambrook, J.A. Eisman, J. Freund, A comparison of longitudinal measurements in the spine and proximal femur using lunar and hologic instruments. J. Bone Miner. Res. **12**(12), 2113–2118 (1997). doi:10.1359/jbmr.1997.12.12.2113
58. J. Makovey, V. Naganathan, P. Sambrook, Gender differences in relationships between body composition components, their distribution and bone mineral density: a cross-sectional opposite sex twin study. Osteoporos. Int. **16**(12), 1495–1505 (2005). doi:10.1007/s00198-005-1841-4
59. G. Mazziotti, J. Bilezikian, E. Canalis, D. Cocchi, A. Giustina, New understanding and treatments for osteoporosis. Endocrine **41**(1), 58–69 (2012). doi:10.1007/s12020-011-9570-2
60. Y. Hamada, S. Kitazawa, R. Kitazawa, K. Kono, S. Goto, H. Komaba, H. Fujii, Y. Yamamoto, H. Yamamoto, M. Usami, M. Fukagawa, The effects of the receptor for advanced glycation end products (RAGE) on bone metabolism under physiological and diabetic conditions. Endocrine **38**(3), 369–376 (2010). doi:10.1007/s12020-010-9390-9
61. J.A. Pasco, M.J. Henry, S. Korn, G.C. Nicholson, M.A. Kotowicz, The metabolic syndrome and bone mineral density in a random sample of Australian men. JMHG. **4**(3), 298–299 (2007)