Follow us @BoneJointRes

Freely available online OPEN ACCESS

BJR

BONE BIOLOGY

The association between selenium and bone health: a meta-analysis

H. Xie,
N. Wang,
H. He,
Z. Yang,
J. Wu,
T. Yang,
Y. Wang

From Xiangya Hospital, Central South University, Changsha, China

Aims

Previous studies have suggested that selenium as a trace element is involved in bone health, but findings related to the specific effect of selenium on bone health remain inconclusive. Thus, we performed a meta-analysis by including all the relevant studies to elucidate the association between selenium status (dietary intake or serum selenium) and bone health indicators (bone mineral density (BMD), osteoporosis (OP), or fracture).

Methods

PubMed, Embase, and Cochrane Library were systematically searched to retrieve relevant articles published before 15 November 2022. Studies focusing on the correlation between selenium and BMD, OP, or fracture were included. Effect sizes included regression coefficient (β), weighted mean difference (WMD), and odds ratio (OR). According to heterogeneity, the fixed-effect or random-effect model was used to assess the association between selenium and bone health.

Results

From 748 non-duplicate publications, 19 studies were included. We found a significantly positive association between dietary selenium intake (β = 0.04, 95% confidence interval (CI) 0.00 to 0.07, p = 0.029) as well as serum selenium (β = 0.13, 95% CI 0.00 to 0.26, p = 0.046) and BMD. Consistently, those with higher selenium intake had a lower risk of OP (OR = 0.47, 95% CI 0.31 to 0.72, p = 0.001), and patients with OP had a significantly lower level of serum selenium than healthy controls (WMD = -2.01, 95% CI -3.91 to -0.12, p = 0.037). High dietary selenium intake was associated with a lower risk of hip fracture (OR = 0.44, 95% CI 0.37 to 0.52, p < 0.001).

Conclusion

Selenium was positively associated with BMD and inversely associated with OP; dietary selenium intake was negatively associated with hip fracture. The causality and therapeutic effect of selenium on OP needs to be investigated in future studies.

Cite this article: *Bone Joint Res* 2023;12(7):423–432.

Keywords: Meta-analysis, Selenium, Osteoporosis, Fracture, Bone mineral density

Article focus

- Evaluate whether selenium status (dietary intake and serum selenium) is a protective factor of bone health.
- The primary outcomes of interest were bone mineral density (BMD), osteoporosis (OP) incidence, and fracture.

Key messages

- Compared with those who had lower dietary selenium intake and lower serum selenium, subjects with higher dietary selenium intake and higher serum selenium had higher BMD.
- Higher dietary selenium intake was associated with a lower risk of OP. Compared with healthy controls, OP patients had lower serum selenium.
- High selenium intake was associated with a lower risk of hip fracture.

Strengths and limitations

- This is the first meta-analysis focusing on the potential association between selenium and bone health.
- Including 19 studies that reported different outcomes of bone health (eight for BMD, eight for OP, and seven for

Correspondence should be sent to Yilun Wang; email: yilun_Wang@csu.edu.cn

doi: 10.1302/2046-3758.127.BJR-2022-0420.R1

Bone Joint Res 2023;12(7):423–432.

fracture), we provided results based on a large sample covering 69,672 subjects.
- Heterogeneity was detected across the studies in certain analyses, while subgroup and sensitivity analyses were not conducted due to the relatively small number of studies.

Introduction

Bone health plays a pivotal role in the quality of life and ability to self-care, and its degradation is observed in diseases such as osteoporosis (OP) and osteoporotic fracture.[1,2] OP is characterized by reduced bone mineral density (BMD) and deterioration of bone microarchitecture, and results in increased bone fragility and risk of fracture,[3] leading to mobility limitations, chronic disability, and reduced quality of life.[4,5] This condition was estimated to affect more than 10 million older adults in the USA,[6] and the prevalence of OP was 20.6% among women aged 40 years or older in China.[7] With an ageing population, it is predicted that OP-related healthcare burdens will increase rapidly.[8] Multiple environmental and genetic factors play a role in OP,[9-11] but there is still an urgent need to determine more modifiable potential risk factors for OP.

Selenium is a trace element that has multiple and complex effects on human health.[12,13] Selenium status was reported to be associated with various disorders such as cardiovascular disease, type 2 diabetes mellitus, infertility, and neurological disease.[14–16] The major source of human selenium is the food chain; geographical variation significantly influences the selenium content and availability in foods, therefore leading to an uneven geographical distribution of selenium-associated diseases.[17,18]

As bones contain the second-highest proportion of selenium in the body,[19] the effects of selenium on bone health have been evaluated in both preclinical and clinical studies.[20,21] Yet, the results of these clinical studies are inconclusive. Meta-analysis can combine the results of multiple scientific studies to obtain a comprehensive estimate. However, no such study had been performed to assess the associations of selenium with BMD, OP, and fracture. We conducted a meta-analysis involving all eligible studies to fill this information gap.

Methods

Protocol and registration. This study was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[22] The protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) network (CRD42019147188). Preplanned methods have been detailed when necessary.[23]

Search strategy. The search was undertaken using the PubMed, Embase, and Cochrane Library databases from inception to 15 November 2022. Key terminology related to selenium (including dietary selenium intake and serum selenium) and bone health (including BMD, OP, and osteoporotic fracture) were used to synthesize the search strategy (Supplementary Table i). The search terms were adapted for different databases accordingly. No restriction was imposed, and non-English written papers were translated. HX and NW independently screened the titles and abstracts. References of the finally included studies were manually reviewed.

Eligibility criteria. Eligibility screening was based on the following inclusion criteria: 1) either interventional or observational studies in humans, including randomized controlled trials (RCTs), case-control studies, cross-sectional studies, and cohort studies; 2) studies using dietary selenium intake or monitoring serum selenium levels; 3) the primary outcome included BMD value, OP (diagnosed based on the World Health Organization (WHO) criteria) and the prevalence or incidence of osteoporotic fracture; and 4) studies reporting the association of selenium with BMD value, OP, or fracture. The exclusion criteria were: 1) animal studies; 2) case reports, meeting abstracts, comments, and reviews; and 3) missing data of interest.

Quality assessment. Methodological quality was assessed by ZY and JW independently. Agreement between them was determined using Cohen's Kappa value and disagreements were resolved by discussion. The Newcastle-Ottawa Scale (NOS),[24] and the adapted NOS for cross-sectional studies, were used for observational studies.[25] The NOS considers three domains, including selection, comparability, and outcome. A study with a score > 7 has high quality, 4 to 6 has moderate quality, and < 4 has low quality. The quality of RCT was rated by the Cochrane risk of bias assessment tool.

Data extraction. The following data were extracted by HX and NW independently using a standardized collection form: publication information (i.e. author, year of publication); study information (i.e. country, study type, study setting); demographic information (i.e. age and sex); exposure information (i.e. dietary selenium intake or serum selenium level); and outcome information (i.e. BMD, prevalence or incidence of OP or fracture). Effect sizes (β, mean difference (MD), odds ratio (OR), or relative risk (RR)) were extracted directly if available, or calculated from the relevant data in the original studies. The data of median and interquartile range were converted to mean and standard deviation (SD) using verified formulae, which were distribution-free of the underlying data.[26] If overall effect sizes were reported, these effect sizes would be extracted. For studies reporting effect sizes by subgroups (e.g. age, sex, BMI, smoking status, alcohol use), the estimates were pooled before conducting meta-analysis. For studies reporting multiple statistical models, the model with the most adjusted variable was extracted.

Statistical analysis. We estimated association between selenium and bone health using the inverse-variant method. Effect sizes were reported as β, WMD, or OR with 95% CI. For studies reporting βs from multiple linear regression models,[27–31] βs were pooled as previously described.[32] The heterogeneity of the included studies was assessed using Cochrane's Q test and I^2 statistics, where $p > 0.05$ for Q statistics and I^2 value < 50% suggested statistical

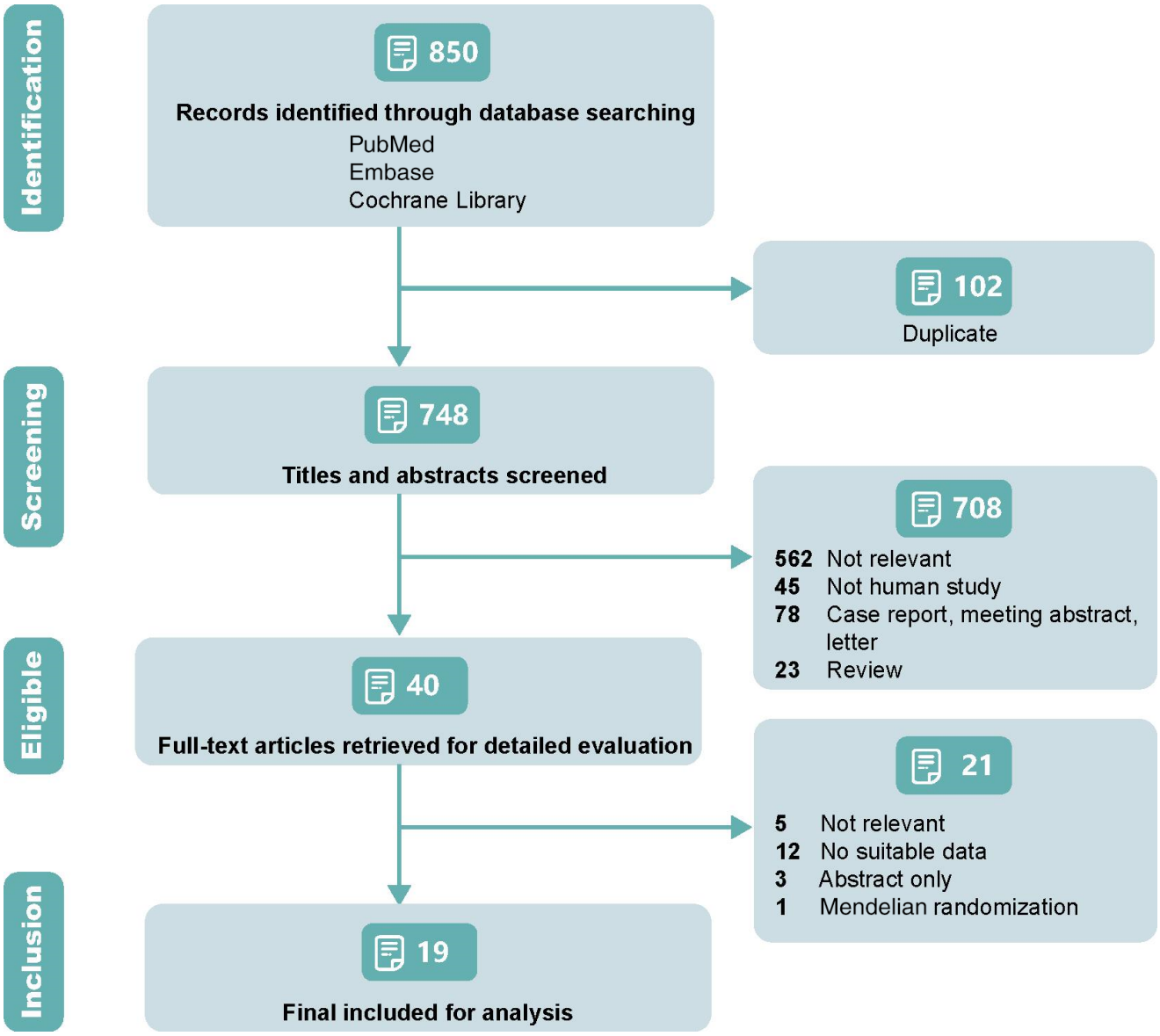

Fig. 1

The selection process of included studies.

homogeneity. If the included studies were homogeneous, the fixed-effect model would be used to pool the data; otherwise, the random-effect model would be used instead. Sensitivity analysis was used to assess the stability of results and the impact of every single study on the pooled estimates. Publication bias would be examined by conducting Egger's test with funnel plot where feasible.[33] All statistical analyses were performed using Stata software (version 12.0; StataCorp, USA) and Comprehensive Meta-Analysis (version 3.3.0; Biostat, USA).

Results

Literature search and characteristics of included studies. After the removal of duplicates, the preliminary literature search yielded 748 articles from PubMed, Embase, and Cochrane Library databases. Eventually, 19 studies covering a total of 69,672 subjects met our inclusion criteria (Figure 1).[27–31,34–47] Of these studies, 18 were observational studies (eight had a cross-sectional design, seven had a case-control design, and three had a prospective design), except for one RCT. Across the included studies, the number of participants ranged from 60 to 21,939, while the mean age varied from 39.4 to 75.8 years, with mean selenium intake ranging from 41.2 to 154.4 μg/d or mean serum selenium level ranging from 66.7 to 131.1 μg/l (Tables I and II). All the observational studies had a NOS score ≥ 4, namely moderate- to high-quality scores. The risk of bias was high for the RCT because of missing outcome data, as it did not include all participants in the analysis (Supplementary Figure a). The agreement between two authors reached a kappa value of 0.902, and

Table I. Characteristics of included studies reporting dietary selenium intake.

Study	Location	Mean age, yrs	Sex	Participants, n	Design	Mean selenium intake, µg/d	Outcome	BMD instrument	BMD or fracture site	Quality score
Grili et al[41] 2022	Brazil	66.8	Female	124	Cross-sectional	154.4	Osteoporosis	DXA	Lumber spine and femur	8
Rivas et al[27] 2012	Spain	-	Female	280	Cross-sectional	75.8	BMD	DXA	Calcaneous	6
Sun et al[39] 2014	China	70.9	Male and female	1,452	Case-control	44.7	Fracture	-	Hip	5
Walsh et al[42] 2021	UK	65.9	Female	120	RCT	-	BMD	DXA	Spine and hip	High risk of bias
Wang et al[38] 2019	China	52.2	Male and female	6,267	Cross-sectional	43.5	Osteoporosis	Radiological absorptiometry system	Middle phalanges of the second to fourth fingers	6
Wolf et al[28] 2005	USA	63.2	Female	11,068	Cross-sectional	85.9	BMD	DXA	Total body, lumbar spine, and total hip	7
Wu et al[29] 2020	USA	-	Male and female	2,983	Cross-sectional	101.5	BMD and fracture	DXA	Spine and femur	8
Xue and Liu[37] 2022	USA	40.68	Male and female	21,939	Cross-sectional	N/A	BMD	DXA	Total body, lumbar spine, and hip	7
Zhang et al[35] 2006	USA	75.8	Male and female	1,215	Case-control	105.7	Fracture	-	Hip	7
Zhang et al[43] 2021	China	42.4	Male and female	17,150	Cohort	41.2	Fracture	-	Total body	5

BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; N/A, not available; RCT, randomized controlled trial.

the overall results are shown in Supplementary Tables ii to iv.

Dietary selenium intake and bone health. Four studies covering 36,270 subjects assessed the correlation between dietary selenium intake and BMD using multiple linear regression models.[27–29,37] The result of the meta-analysis revealed a positive association between dietary selenium intake and BMD (β = 0.04, 95% confidence interval (CI) 0.00 to 0.07, p = 0.029, I^2 = 95.91) (Figure 2a).

Two cross-sectional studies addressed the relationship between dietary selenium intake and OP involving 6,391 participants.[38,41] The result of the meta-analysis suggested a negative association between dietary selenium intake and OP (OR = 0.47, 95% CI 0.31 to 0.72; p = 0.001, I^2 = 0) (Figure 2b). This was consistent with our finding that dietary selenium intake was positively associated with BMD.

Four studies covering 24,325 subjects reported the use of logistic regression models for evaluating the effect of dietary selenium intake on total fracture risk.[29,35,39,43] The result of the meta-analysis did not reveal a statistically significant association between dietary selenium intake and total fracture risk (OR = 0.64, 95% CI 0.29 to 1.39; p = 0.261) (Supplementary Figure b). Egger's test demonstrated no evidence of publication bias (p = 0.528). For hip fracture, meta-analysis of three studies covering 21,585 participants suggested that high dietary selenium intake was associated with lower risk of hip fracture (OR = 0.44, 95% CI 0.37 to 0.52; p < 0.001) (Figure 2c).[29,35,39] An I^2 = 65.2 suggested significant heterogeneity.

Serum selenium and bone health. Four studies covering 3,370 subjects reported the use of multiple linear regression models for evaluating the association between serum selenium and BMD.[29–31,47] The result of the meta-analysis suggested a significantly positive association between serum selenium and BMD (β = 0.13, 95% CI 0.00 to 0.26; p = 0.046, I^2 = 86.60) (Figure 3a).

Five case-control studies covering 508 subjects reported the difference of serum selenium between OP and healthy subjects.[34,40,44–46] The result from the random-effect model did not support a statistically significant difference of serum selenium between OP patients and healthy controls (WMD = -7.48, 95% CI -15.81 to 0.84; p = 0.078). To assess the stability of the result and the

Table II. Characteristics of included studies reporting serum selenium.

Study	Location	Mean age, yrs	Sex	Participants, n	Design	Mean serum selenium, µg/l	Outcome	BMD instrument	BMD or fracture site	Quality score
Al-E-Ahmad et al[34] 2018	India	67.2	Male and female	180	Case-control	57.6	Osteoporosis	DXA	Spine and femur	7
Arikan et al[45] 2011	Turkey	54.7	Male and female	70	Case-control	66.7	Osteoporosis	DXA	Lumbar spine, femoral neck, trochanter, Ward's triangle, and total hip	5
Beukhof et al[47] 2016	Netherlands	77	Male	387	Cross-sectional	91.9	BMD	DXA	Femoral neck, trochanter, Ward's triangle	7
Galvez-Fernandez et al[36] 2021	Spain	48.7	Male and female	1,365	Cohort	84.7	Fracture	Radiograph, CT scan, or nuclear magnetic resonance	Hip, humerus, and Colle's fracture	6
Hoeg et al[31] 2012	Europe	67.8	Female	2,374	Cohort	94.3	Osteoporosis and fracture	DXA	Lumbar spine, femoral neck	8
Kul et al[46] 2021	Turkey	64.8	Female	75	Case-control	261.2	Osteoporosis	DXA	Lumbar vertebrae, femoral neck	6
Wang et al[40] 2015	China	65.5	Male	60	Case-control	129.8	Osteoporosis	DXA	Lumbar spine, femoral neck, trochanter, Ward's triangle	6
Odabasi et al[44] 2008	Turkey	60.5	Female	138	Case-control	76.9	Osteoporosis	DXA	Lumbar vertebrae	5
Wei et al[30] 2021	USA	39.4	Male and female	2,545	Cross-sectional	128.9	BMD	DXA	Lumbar vertebrae and total BMDs	7
Wu et al[29] 2020	USA	-	Male and female	2,983	Cross-sectional	131.1	BMD and fracture	DXA	Spine and femur	8

BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry.

influence of each study, we performed a sensitivity analysis. Sequentially omitting each single study from the meta-analysis did not significantly alter the estimate reported by overall analysis except for Al-E-Ahmad et al[34] (MD = -23.51, 95% CI -30.98 to -16.04; $p < 0.001$). After excluding it, the meta-analysis revealed a statistically significant association between serum selenium and OP, indicating that OP patients had lower serum selenium level than healthy controls (WMD = -2.01, 95% CI -3.91 to -0.12; $p = 0.037$, $I^2 = 0$) (Figure 3b). The result of Egger's test did not demonstrate evidence of publication bias ($p = 0.406$).

Three studies reported the association between serum selenium and fracture risk. Two of them had a prospective design,[31,36] while the remaining one had a cross-sectional design.[29] The pooled result of two prospective studies did not reveal a statistically significant association between serum selenium and hip fracture risk (HR = 1.43, 95% CI 0.68 to 3.03; $p = 0.350$, $I^2 = 75.74$) (Figure 3c). The cross-sectional study reported an inverse association between serum selenium and history of any fracture (OR = 0.18, 95% CI 0.01 to 0.57; $p = 0.006$).

Effect of selenium supplementation on bone health. The effect of selenium supplementation on bone health was

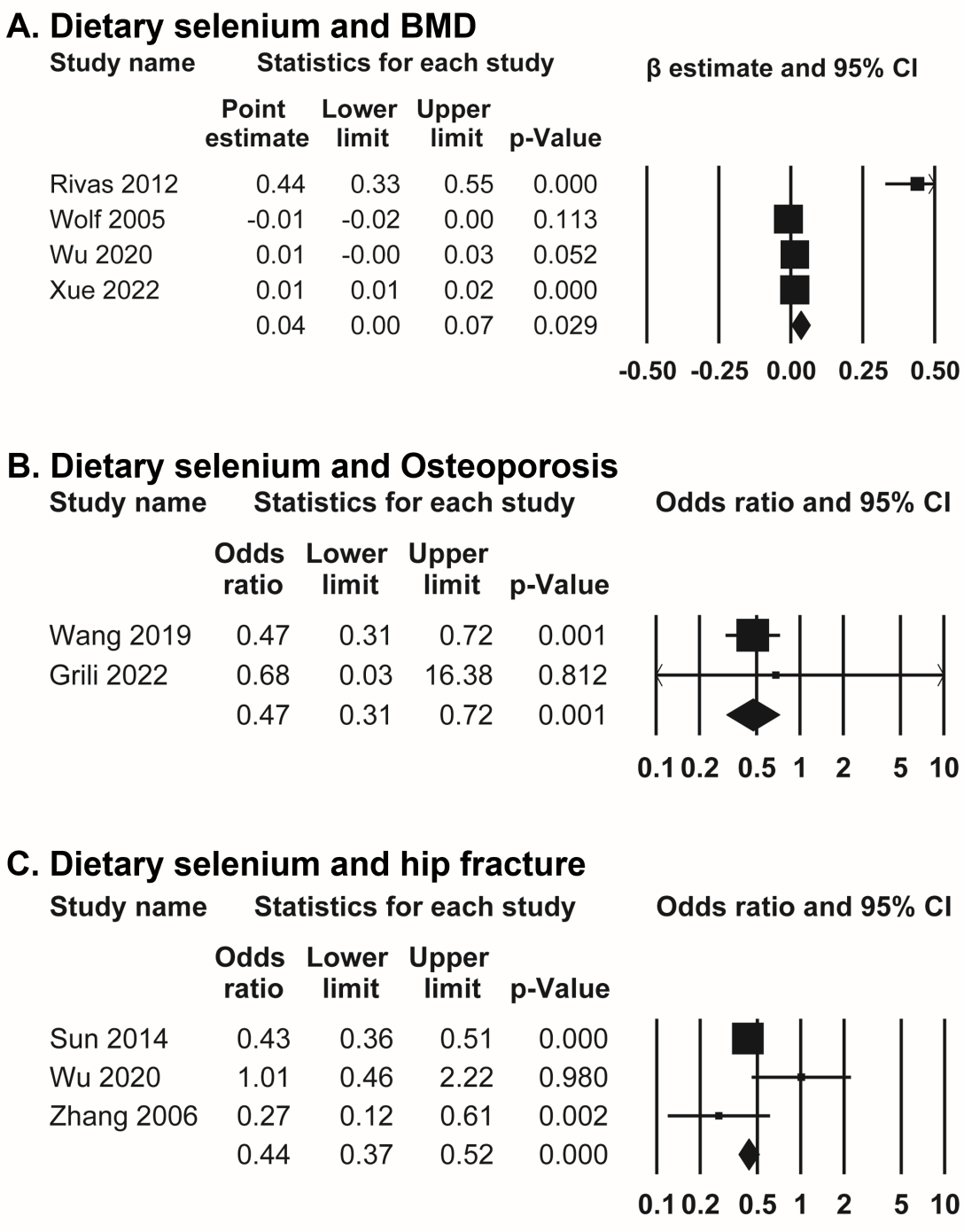

Fig. 2

Forest plots of association between dietary selenium and bone health. a) Association between dietary selenium intake and bone mineral density (BMD). b) Association between dietary selenium intake and prevalence of osteoporosis. c) Association between dietary selenium intake and fracture. CI, confidence interval.

evaluated by one RCT. By recruiting 120 postmenopausal women with osteopenia or OP and randomly assigning them 1:1:1 to receive selenite 200 μg, 50 μg, or placebo orally once a day, this RCT demonstrated no evidence of BMD improvement after six-month follow-up.[42]

Discussion

To our best knowledge, this is the first meta-analysis to comprehensively explore the effect of selenium on bone health. The present meta-analysis shows that dietary selenium intake and serum selenium were both positively

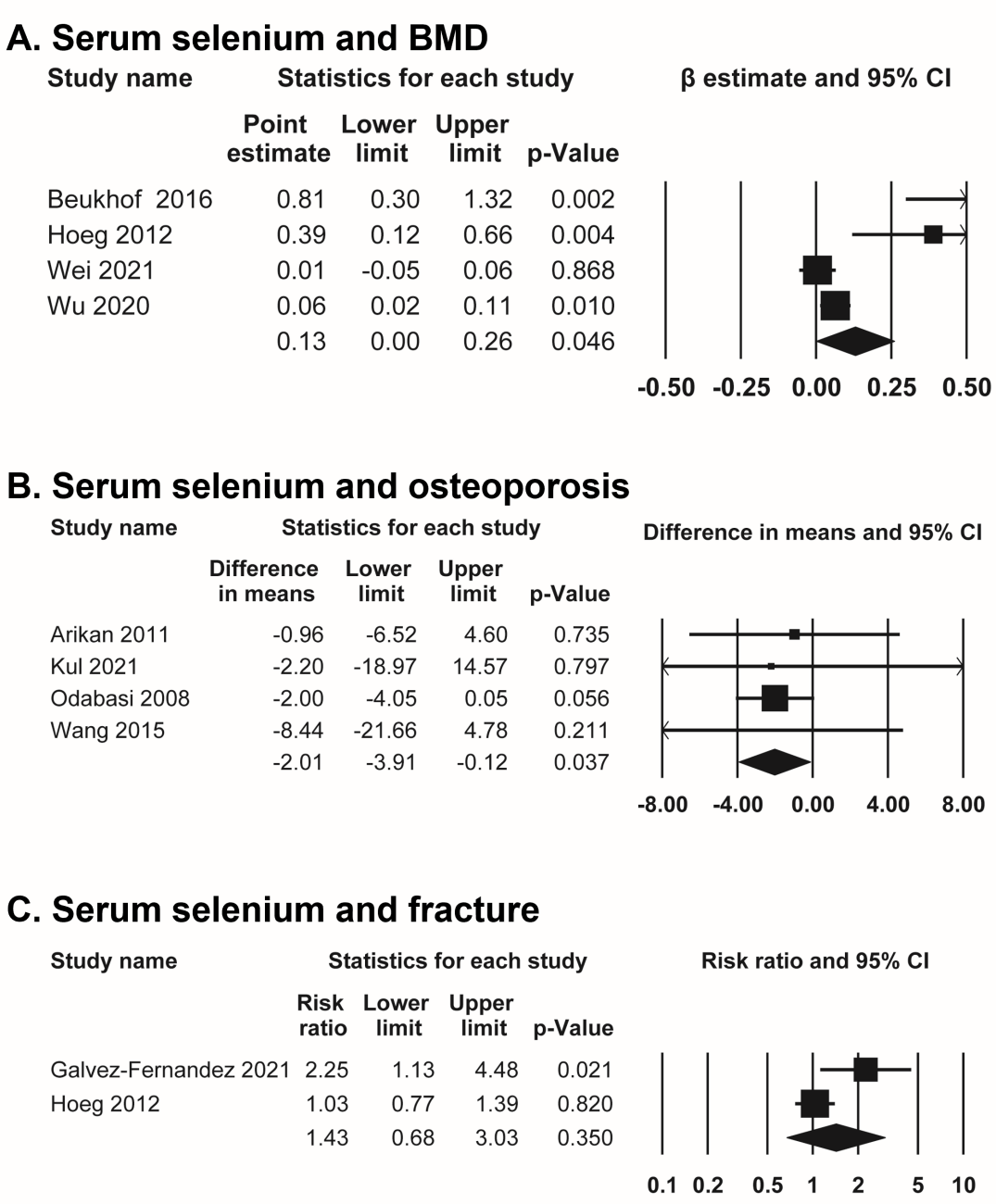

Fig. 3

Forest plots of association between serum selenium and bone health. a) Association between serum selenium and bone mineral density (BMD). b) Difference of serum selenium level between osteoporosis patients and non-osteoporosis controls. c) Association between serum selenium and osteoporotic fracture risk. CI, confidence interval.

correlated with BMD; high selenium intake was negatively associated with risk of OP and hip fracture, and OP patients had lower serum selenium than healthy controls. Nevertheless, no significant association was found between serum selenium with fracture rate.

Comparison with previous studies. A narrative review by Yang et al[20] highlighted the importance of selenium in bone health, but they did not perform a meta-analysis and could not provide precise estimates of the effect. Results from Mendelian randomization, a technique believed less likely to suffer from confounding factors, revealed a positive association only between serum selenium and heel BMD.[48] In our analysis, we included all the eligible studies and found that selenium may be protective for BMD, OP, and hip fracture.

Possible explanations. Selenium is an essential trace element for protecting cells against oxidative damage; selenium deficiency increases the risk of disorders including

cardiovascular disease,[49] cancer,[50] hepatopathy,[51] and arthropathy.[12] Given its antioxidant effect, selenium has been reported as a potential protective factor for osteoarthritis (OA) and rheumatoid arthritis (RA),[52–54] and a preclinical study has shown a promising therapeutic effect of selenium nanoparticles in RA-induced animals.[55] Given that oxidative stress has been suggested as destructive to bone,[56–58] it is reasonable to speculate that selenium has a protective effect on BMD as well as on OP. Since selenium status was positively associated with BMD, an inverse association between selenium and fracture susceptibility was expected. Indeed, the present meta-analysis found a significant association between dietary selenium intake and hip fracture; however, no association between serum selenium and fracture risk was found. One possible explanation may be that low BMD is just one among a cluster of important risk factors for fracture.[59–61] Moreover, in one prospective study, only a small number of fractures were recorded during the follow-up.[31] Therefore, prospective studies with longer follow-up and a larger number of participants are required to substantiate the link between selenium and fracture. The only RCT included in this work concluded that sodium selenite supplementation for six months did not benefit bone health in postmenopausal women with osteopenia or OP.[42] However, it only involved postmenopausal women who had normal serum selenium levels (not less than 70 μg/l)[62] at baseline. Thus, it is unknown whether the effect of selenium on BMD would vary in different age groups, males, or those with selenium deficiency. Notably, this research did not find different risks of adverse events between the two groups receiving different doses of selenium, providing evidence for the safety of selenium supplementation in the population with normal serum selenium.

Strength and limitations. The present study has several strengths. First, a systematic literature search strategy was designed and implemented to capture all eligible studies. Second, two indicators of selenium status and three indicators of bone health were considered (including BMD, OP, and fracture), taking into account both OP and its consequences, to comprehensively assess the effect of selenium on bone health. Third, stringent inclusion and exclusion criteria were followed to eliminate irrelevant and low-quality studies, making the results more reliable.

Nevertheless, the limitations of our study should also be acknowledged. First, the meta-analysis was based on observational studies that are susceptible to bias. Second, the number of included studies was relatively small for certain analyses, so we failed to run subgroup analyses as mentioned in the protocol and assess publication bias for all outcomes.[33,63] Third, heterogeneity was detected across the studies in certain analyses, which can be partly explained by study design, regional difference, population variability, various methods for selenium and BMD measurement, and varying bioavailability of dietary selenium intake.

Clinical and research implications. Sufficient nutritional intake is important for preventing and treating OP.[2,3,64] As an essential trace element for human health,[65] the effect of selenium on bone health was inconclusive. Our meta-analysis demonstrated a significant association of selenium with BMD, OP, and hip fracture, without any significant association between serum selenium and fracture, indicating that there may be a more intricate mechanism underlying their relationship. This meta-analysis could help to resolve controversy and uncertainty among previous studies and provide evidence supporting the protective role of selenium on OP, which would serve as a foundation for future research to assess causality and investigate the potential of selenium as an adjuvant therapy for OP. Moreover, our work identified some information gaps in the association between selenium and bone health. Since it was reported that selenium had a dose-response effect on mortality and type 2 diabetes mellitus,[14,66] a potential dose-response effect of selenium on bone health could not be ruled out, and more researches are needed to elucidate it. Furthermore, most studies involved participants without evidence of selenium deficiency; future studies should focus on the population with selenium deficiency or relatively low selenium levels.

In summary, this meta-analysis found that selenium was positively associated with BMD, and serum selenium was inversely associated with OP in the population with relative normal selenium. Dietary selenium intake was negatively associated with risk of hip fracture. Future studies are warranted to confirm this effect on populations with different selenium levels.

Supplementary material

Tables showing complete search strategy and the results of quality assessment for included studies. Figures showing a risk of bias graph for randomized controlled trial and a forest plot of the association between dietary selenium and any fractures.

References

1. **Rizzoli R**, **Biver E**, **Brennan-Speranza TC**. Nutritional intake and bone health. *Lancet Diabetes Endocrinol*. 2021;9(9):606–621.
2. **Hampton T**. Experts urge early investment in bone health. *JAMA*. 2004;291(7):811–812.
3. **NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy**. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001;285(6):785–795.
4. **Crandall CJ**, **Ensrud KE**. Osteoporosis screening in younger postmenopausal women. *JAMA*. 2020;323(4):367–368.
5. **Alcock H**, **Moppett EA**, **Moppett IK**. Early mortality outcomes of patients with fragility hip fracture and concurrent SARS-CoV-2 infection: a systematic review and meta-analysis. *Bone Jt Open*. 2021;2(5):314–322.
6. **Wright NC**, **Looker AC**, **Saag KG**, **et al**. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res*. 2014;29(11):2520–2526.
7. **Wang L**, **Yu W**, **Yin X**, **et al**. Prevalence of osteoporosis and fracture in China: The China Osteoporosis Prevalence Study. *JAMA Netw Open*. 2021;4(8):e2121106.
8. **Burge R**, **Dawson-Hughes B**, **Solomon DH**, **Wong JB**, **King A**, **Tosteson A**. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res*. 2007;22(3):465–475.

9. **Cheng B**, **Wen Y**, **Yang X**, **et al**. Gut microbiota is associated with bone mineral density: an observational and genome-wide environmental interaction analysis in the UK Biobank cohort. *Bone Joint Res*. 2021;10(11):734–741.
10. **Jia Y**, **Qi X**, **Ma M**, **et al**. Integrating genome-wide association study with regulatory SNP annotations identified novel candidate genes for osteoporosis. *Bone Joint Res*. 2023;12(2):147–154.
11. **Li J**, **Ho WTP**, **Liu C**, **et al**. The role of gut microbiota in bone homeostasis. *Bone Joint Res*. 2021;10(1):51–59.
12. **Kang D**, **Lee J**, **Wu C**, **et al**. The role of selenium metabolism and selenoproteins in cartilage homeostasis and arthropathies. *Exp Mol Med*. 2020;52(8):1198–1208.
13. **Winther KH**, **Rayman MP**, **Bonnema SJ**, **Hegedüs L**. Selenium in thyroid disorders - essential knowledge for clinicians. *Nat Rev Endocrinol*. 2020;16(3):165–176.
14. **Wang X-L**, **Yang T-B**, **Wei J**, **Lei G-H**, **Zeng C**. Association between serum selenium level and type 2 diabetes mellitus: a non-linear dose-response meta-analysis of observational studies. *Nutr J*. 2016;15(1):48.
15. **Shahar A**, **Patel KV**, **Semba RD**, **et al**. Plasma selenium is positively related to performance in neurological tasks assessing coordination and motor speed. *Mov Disord*. 2010;25(12):1909–1915.
16. **Sajjadi SS**, **Foshati S**, **Haddadian-Khouzani S**, **Rouhani MH**. The role of selenium in depression: a systematic review and meta-analysis of human observational and interventional studies. *Sci Rep*. 2022;12(1):1045.
17. **Dinh QT**, **Cui Z**, **Huang J**, **et al**. Selenium distribution in the Chinese environment and its relationship with human health: A review. *Environ Int*. 2018;112:294–309.
18. **Johnson CC**, **Fordyce FM**, **Rayman MP**. Symposium on "Geographical and geological influences on nutrition": Factors controlling the distribution of selenium in the environment and their impact on health and nutrition. *Proc Nutr Soc*. 2010;69(1):119–132.
19. **Zachara BA**, **Pawluk H**, **Bloch-Boguslawska E**, **et al**. Tissue level, distribution, and total body selenium content in healthy and diseased humans in Poland. *Arch Environ Health*. 2001;56(5):461–466.
20. **Yang T**, **Lee S-Y**, **Park K-C**, **Park S-H**, **Chung J**, **Lee S**. The effects of selenium on bone health: From element to therapeutics. *Molecules*. 2022;27(2):392.
21. **Zeng H**, **Cao JJ**, **Combs GF**. Selenium in bone health: roles in antioxidant protection and cell proliferation. *Nutrients*. 2013;5(1):97–110.
22. **Moher D**, **Liberati A**, **Tetzlaff J**, **Altman DG**, **PRISMA Group**. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
23. **Wang N**, **Xie D**, **Wu J**, **et al**. Selenium and bone health: a protocol for a systematic review and meta-analysis. *BMJ Open*. 2020;10(10):e036612.
24. **Wells GA**, **Shea B**, **O'Connell D**, **et al**. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
25. **Deeks JJ**, **Dinnes J**, **D'Amico R**, **et al**. Evaluating non-randomised intervention studies. *Health Technol Assess*. 2003;7(27):iii–x.
26. **Wan X**, **Wang W**, **Liu J**, **Tong T**. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.
27. **Rivas A**, **Romero A**, **Mariscal-Arcas M**, **et al**. Association between dietary antioxidant quality score (DAQs) and bone mineral density in Spanish women. *Nutr Hosp*. 2012;27(6):1886–1893.
28. **Wolf RL**, **Cauley JA**, **Pettinger M**, **et al**. Lack of a relation between vitamin and mineral antioxidants and bone mineral density: results from the Women's Health Initiative. *Am J Clin Nutr*. 2005;82(3):581–588.
29. **Wu CC**, **Wang CK**, **Yang AM**, **Lu CS**, **Lin CY**. Selenium status is independently related to bone mineral density, FRAX score, and bone fracture history: NHANES, 2013 to 2014. *Bone*. 2021;143:115631.
30. **Wei M-H**, **Cui Y**, **Zhou H-L**, **et al**. Associations of multiple metals with bone mineral density: A population-based study in US adults. *Chemosphere*. 2021;282:131150.
31. **Hoeg A**, **Gogakos A**, **Murphy E**, **et al**. Bone turnover and bone mineral density are independently related to selenium status in healthy euthyroid postmenopausal women. *J Clin Endocrinol Metab*. 2012;97(11):4061–4070.
32. **Ramsey KA**, **Rojer AGM**, **D'Andrea L**, **et al**. The association of objectively measured physical activity and sedentary behavior with skeletal muscle strength and muscle power in older adults: A systematic review and meta-analysis. *Ageing Res Rev*. 2021;67:101266.
33. **Dalton JE**, **Bolen SD**, **Mascha EJ**. Publication bias: The elephant in the review. *Anesth Analg*. 2016;123(4):812–813.
34. **Al-E-Ahmad A**, **Parsian H**, **Fathi M**, **et al**. ALOX12 gene polymorphisms and serum selenium status in elderly osteoporotic patients. *Adv Clin Exp Med*. 2018;27(12):1717–1722.
35. **Zhang J**, **Munger RG**, **West NA**, **Cutler DR**, **Wengreen HJ**, **Corcoran CD**. Antioxidant intake and risk of osteoporotic hip fracture in Utah: an effect modified by smoking status. *Am J Epidemiol*. 2006;163(1):9–17.
36. **Galvez-Fernandez M**, **Grau-Perez M**, **Garcia-Barrera T**, **et al**. Arsenic, cadmium, and selenium exposures and bone mineral density-related endpoints: The HORTEGA study. *Free Radic Biol Med*. 2021;162:392–400.
37. **Xue G**, **Liu R**. Association between dietary selenium intake and bone mineral density in the US general population. *Ann Transl Med*. 2022;10(16):869.
38. **Wang Y**, **Xie D**, **Li J**, **et al**. Association between dietary selenium intake and the prevalence of osteoporosis: a cross-sectional study. *BMC Musculoskelet Disord*. 2019;20(1):585.
39. **Sun L**, **Li B**, **Xie H**, **et al**. Associations between the dietary intake of antioxidant nutrients and the risk of hip fracture in elderly Chinese: a case-control study. *Br J Nutr*. 2014;112(10):1706–1714.
40. **Wang L**, **Yu H**, **Yang G**, **et al**. Correlation between bone mineral density and serum trace element contents of elderly males in Beijing urban area. *Int J Clin Exp Med*. 2015;8(10):19250–19257.
41. **Grili PP da F**, **Vidigal CV**, **da Cruz GF**, **et al**. Dietary consumption of selenium inversely associated with osteoporosis in postmenopausal women. *Front Nutr*. 2022;9:997414.
42. **Walsh JS**, **Jacques RM**, **Schomburg L**, **et al**. Effect of selenium supplementation on musculoskeletal health in older women: a randomised, double-blind, placebo-controlled trial. *Lancet Healthy Longev*. 2021;2(4):e212–e221.
43. **Zhang Y**, **Ye M**, **Zhao Y**, **et al**. Higher dietary Se intake is associated with the risk of new-onset fracture: A national longitudinal study for 20 years. *Front Nutr*. 2021;8:719147.
44. **Odabasi E**, **Turan M**, **Aydin A**, **Akay C**, **Kutlu M**. Magnesium, zinc, copper, manganese, and selenium levels in postmenopausal women with osteoporosis. Can magnesium play a key role in osteoporosis? *Ann Acad Med Singap*. 2008;37(7):564–567.
45. **Arikan DC**, **Coskun A**, **Ozer A**, **Kilinc M**, **Atalay F**, **Arikan T**. Plasma selenium, zinc, copper and lipid levels in postmenopausal Turkish women and their relation with osteoporosis. *Biol Trace Elem Res*. 2011;144(1–3):407–417.
46. **Kul A**, **Bayraktutan Z**, **Çelik M**. The relationship between bone mineral density values and prognostic nutritional index as well as serum trace element levels in postmenopausal women. *Turk J Osteoporos*. 2021;27(2):82–89.
47. **Beukhof CM**, **Medici M**, **van den Beld AW**, **et al**. Selenium status is positively associated with bone mineral density in healthy aging European men. *PLoS One*. 2016;11(4):e0152748.
48. **Qu Z**, **Yang F**, **Yan Y**, **et al**. Relationship between serum nutritional factors and bone mineral density: A Mendelian randomization study. *J Clin Endocrinol Metab*. 2021;106(6):e2434–e2443.
49. **Zhang X**, **Liu C**, **Guo J**, **Song Y**. Selenium status and cardiovascular diseases: meta-analysis of prospective observational studies and randomized controlled trials. *Eur J Clin Nutr*. 2016;70(2):162–169.
50. **Willett WC**, **Polk BF**, **Morris JS**, **et al**. Prediagnostic serum selenium and risk of cancer. *Lancet*. 1983;2(8342):130–134.
51. **Guo C-H**, **Chen P-C**, **Ko W-S**. Status of essential trace minerals and oxidative stress in viral hepatitis C patients with nonalcoholic fatty liver disease. *Int J Med Sci*. 2013;10(6):730–737.
52. **Wang N**, **Xie M**, **Lei G**, **et al**. A cross-sectional study of association between plasma selenium levels and the prevalence of osteoarthritis: Data from the Xiangya Osteoarthritis Study. *J Nutr Health Aging*. 2022;26(2):197–202.
53. **Qamar N**, **John P**, **Bhatti A**. Emerging role of selenium in treatment of rheumatoid arthritis: An insight on its antioxidant properties. *J Trace Elem Med Biol*. 2021;66:126737.
54. **Turrubiates-Hernández FJ**, **Márquez-Sandoval YF**, **González-Estevez G**, **Reyes-Castillo Z**, **Muñoz-Valle JF**. The relevance of selenium status in rheumatoid arthritis. *Nutrients*. 2020;12(10):3007.
55. **Liu Y**, **Ma L**, **Zhou H**, **et al**. Polypeptide nano-Se targeting inflammation and theranostic rheumatoid arthritis by anti-angiogenic and NO activating AMPKα signaling pathway. *J Mater Chem B*. 2018;6(21):3497–3514.
56. **Kimball JS**, **Johnson JP**, **Carlson DA**. Oxidative stress and osteoporosis. *J Bone Joint Surg Am*. 2021;103-A(15):1451–1461.
57. **Reeves MA**, **Hoffmann PR**. The human selenoproteome: recent insights into functions and regulation. *Cell Mol Life Sci*. 2009;66(15):2457–2478.
58. **Manolagas SC**. From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. *Endocr Rev*. 2010;31(3):266–300.
59. **Compston JE**, **McClung MR**, **Leslie WD**. Osteoporosis. *Lancet*. 2019;393(10169):364–376.

60. **Schuit SCE**, **van der Klift M**, **Weel AEAM**, **et al**. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. *Bone*. 2004;34(1):195–202.
61. **Siris ES**, **Chen Y-T**, **Abbott TA**, **et al**. Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med*. 2004;164(10):1108–1112.
62. **Moffat AC**, **Osselton DM**, **Widdop B**, **Watts J**. *Clarke's Analysis of Drugs and Poisons*. 2011.
63. **Cuijpers P**, **Griffin JW**, **Furukawa TA**. The lack of statistical power of subgroup analyses in meta-analyses: a cautionary note. *Epidemiol Psychiatr Sci*. 2021;30:e78.
64. **Borer KT**. Physical activity in the prevention and amelioration of osteoporosis in women: interaction of mechanical, hormonal and dietary factors. *Sports Med*. 2005;35(9):779–830.
65. **Rayman MP**. Selenium and human health. *Lancet*. 2012;379(9822):1256–1268.
66. **Heyland DK**, **Dhaliwal R**, **Suchner U**, **Berger MM**. Antioxidant nutrients: a systematic review of trace elements and vitamins in the critically ill patient. *Intensive Care Med*. 2005;31(3):327–337.

Author information:
- H. Xie, MBBS, Postgraduate Student
- N. Wang, MBBS, PhD Candidate
- H. He, MBBS, PhD Candidate
  Department of Orthopaedics, Xiangya Hospital, Central South University, Changsha, China.
- Z. Yang, MSc, Research Technician
- J. Wu, MSc, Research Technician
  Hunan Key Laboratory of Joint Degeneration and Injury, Xiangya Hospital, Central South University, Changsha, China; Key Laboratory of Aging-related Bone and Joint Diseases Prevention and Treatment, Ministry of Education, Xiangya Hospital, Central South University, Changsha, China.
- T. Yang, MD, Radiologist, Key Laboratory of Aging-related Bone and Joint Diseases Prevention and Treatment, Ministry of Education, Xiangya Hospital, Central South University, Changsha, China; Health Management Center, Xiangya Hospital, Central South University, Changsha, China.
- Y. Wang, MD, Orthopaedic Surgeon, Department of Orthopaedics, Xiangya Hospital, Central South University, Changsha, China; Hunan Key Laboratory of Joint Degeneration and Injury, Xiangya Hospital, Central South University, Changsha, China; Key Laboratory of Aging-related Bone and Joint Diseases Prevention and Treatment, Ministry of Education, Xiangya Hospital, Central South University, Changsha, China; National Clinical Research Center of Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, China.

Author contributions:
- H. Xie: Data curation, Formal analysis, Writing – original draft, Visualization.
- N. Wang: Data curation, Formal analysis, Writing – original draft, Visualization.
- H. He: Methodology, Investigation.
- Y. Zidan: Methodology, Investigation.
- J. Wu: Methodology, Investigation.
- T. Yang: Conceptualization, Validation, Supervision, Writing – review & editing.
- Y. Wang: Conceptualization, Validation, Supervision, Writing – review & editing.

- H. Xie and N. Wang are joint first authors.

- T. Yang and Y. Wang are joint senior authors.

Funding statement:
- The authors disclose receipt of the following financial or material support for the research, authorship, and/or publication of this article: this work was supported by the Youth Science Foundation of Xiangya Hospital (2021Q14) and the Natural Science Foundation of Hunan Province (2022JJ40821).

Data sharing:
- All data generated or analyzed during this study are included in the published article and/or in the supplementary material.

Acknowledgements:
- Everyone who contributed significantly to the work has been listed as an author.

Open access funding:
- The authors confirm that the open access fee for this study was self-funded.