Effects of vitamin K supplementation on bone mineral density at different sites and bone metabolism in the middle-aged and elderly population

a meta-analysis and systematic review of randomized controlled trials

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Aims

This meta-analysis and systematic review aimed to comprehensively investigate the effects of vitamin K supplementation on bone mineral density (BMD) at various sites and bone metabolism in middle-aged and older adults.

Methods

The databases of PubMed, Web of Science, and Cochrane Library were thoroughly searched from inception to July 2023.

Results

The results revealed that vitamin K supplementation increased BMD at the lumbar spine ($p = 0.035$). Moreover, the pooled effects demonstrated a notable increase in carboxylated osteocalcin (cOC) ($p = 0.004$), a decrease in uncarboxylated osteocalcin (ucOC) ($p < 0.001$), and no significant effect on total osteocalcin (tOC) ($p = 0.076$). Accordingly, the ratio of cOC to ucOC ($p = 0.002$) significantly increased, while the ratio of ucOC to tOC decreased ($p = 0.043$). However, there was no significant effect of vitamin K supplementation on other bone metabolism markers, such as cross-linked telopeptide of type 1 collagen (NTx), bone alkaline phosphatase (BAP), and procollagen I N-terminal propeptide (PINP). Subgroup analysis revealed that vitamin K notably enhanced bone health in females by increasing lumbar spine BMD ($p = 0.028$) and decreasing ucOC ($p < 0.001$). Vitamin K, especially vitamin K2, exhibited effects on maintaining or increasing lumbar spine BMD, and influencing the balance of cOC and ucOC.

Conclusion

This review suggests that the beneficial effects of vitamin K supplementation on bone health primarily involve enhancing the carboxylation of OC rather than altering the total amount of OC.

Bone & Joint Research

Article focus

- What are the effects of vitamin K supplementation on bone mineral density (BMD) at various sites in middle-aged and older adults?
- Which bone markers are affected by vitamin K supplementation?

Key messages

- This meta-analysis and systematic review highlights that vitamin K, especially vitamin K2, maintains or increases lumbar spine BMD in middle-aged and elderly people.
- These effects may be achieved mainly through increasing the conversion of uncarboxylated osteocalcin (ucOC) to carboxylated osteocalcin (cOC).
- There was no effect on total osteocalcin (tOC), cross-linked telopeptide of type 1 collagen (NTx), bone alkaline phosphatase (BAP), and procollagen I N-terminal propeptide (PINP).

Strengths and limitations

- The inclusion of five indicators of BMD and eight bone metabolism indicators in this study offered a comprehensive assessment of the effect of vitamin K on BMD and bone metabolism in middle-aged and elderly individuals.
- The detailed subgroup analysis provided substantial evidence for exploring heterogeneity within the data.
- Some indicators, such as PINP and NTx, were only present in a limited number of studies. Data on means and SDs were sometimes only available in graphical format, potentially introducing statistical bias.
- Some studies involved the combination of vitamin K with other medications, calcium or vitamin D, which could have magnified the effects attributed to vitamin K.
- Due to constraints in population intervention studies, in-depth discussions on the underlying mechanisms were limited.

Introduction

Bone-related diseases, such as osteoporosis (OP) and osteoarthritis (OA), present significant global public health challenges. The worldwide prevalence of OP and OA is estimated to affect approximately 200 million and 527 million patients, respectively.[1,2] OP is particularly common in patients undergoing total hip arthroplasty (THA) and contributes to over 8.9 million fractures annually.[3,4] Studies indicate a fracture risk of one in three women and one in five men;[5] there is a notable risk of refracture during the post-fracture recovery period.[6] With the global population ageing, the health of middle-aged and elderly individuals is of growing concern. Effective prevention and management of bone-related diseases play an important role in the quality of life in this demographic. Among the various treatments, dietary interventions are increasingly recognized as pivotal in the prevention and management of bone-related diseases.[7,8]

Several studies have suggested that vitamin K plays a significant role in bone health.[9,10] Vitamin K, a crucial fat-soluble nutrient, exists in two primary forms: vitamin K1 (phylloquinone), which is predominantly found in green vegetables, vegetable oils, or fruits; and vitamin K2, which is present in animal and fermented foods and is synthesized by gut bacteria.[11–13] The main supplementation forms of vitamin K2 are MK-7 and MK-4. Vitamin K facilitates the carboxylation of vitamin K-dependent proteins (VKDP), essential for bone metabolism.[8,12] Osteocalcin (OC), a VKDP, serves as a key biomarker of bone metabolism and formation. Vitamin K acts as a cofactor in the carboxylation process of osteocalcin, converting it into carboxylated osteocalcin (cOC), which plays a crucial role in bone mineralization by promoting the binding of calcium and hydroxyapatite. Conversely, uncarboxylated osteocalcin (ucOC) is recognized as a sensitive indicator of vitamin K deficiency.[14–16] A 2015 meta-analysis showed that vitamin K supplementation can reduce levels of ucOC.[17] Other markers of bone metabolism, such as procollagen I N-terminal propeptide (PINP), bone alkaline phosphatase (BAP), and cross-linked telopeptide of type 1 collagen (NTx), offer insights into bone turnover. PINP, for instance, reflects the synthesis of new collagen by osteoblasts and is recommended for assessing fracture risk and monitoring osteoporosis. Research indicates a significant increase in serum PINP levels six to 12 weeks post tibial and femoral stem fractures.[18] BAP levels correlate with osteoblast activity, while NTx is associated with bone resorption.[19,20] However, the effects of vitamin K supplementation on these markers remain inconsistent. Bone mineral density is widely acknowledged as a key indicator of bone strength, with some studies highlighting a significant relationship between vitamin K and bone mineral density.[21–23] A randomized controlled trial (RCT) has also revealed that the supplementation of vitamin K2 can improve female bone mineral density (BMD) in their waist and hips.[24] Nevertheless, conflicting findings exist, as some research suggests that vitamin K supplementation may only help maintain lumbar spine BMD, without increasing it.[25] Consequently, the influence of vitamin K on BMD at different skeletal sites remains inconclusive.

Despite several meta-analyses on vitamin K and bone health, the focus has mainly been on postmenopausal women, and the effects of vitamin K on BMD have yielded inconsistent results.[17,26,27] In addition, there is also a lack of systematic evaluation of the effects of vitamin K on different bone sites and markers of bone metabolism. This study aims to provide a comprehensive summary of the effects of vitamin K supplementation on bone mineral density (BMD) at different skeletal sites in middle-aged and elderly individuals, as well as to analyze the impact of different vitamin K species on bone metabolic indexes such as OC, NTx, BAP, and PINP. This will enable a more comprehensive and systematic understanding of the role of vitamin K in bone health.

Methods

Study selection strategy

This meta-analysis was completed according to the PRISMA checklist and was registered through PROSPERO (CRD42023432432). Articles were identified through PubMed, Web of Science, and Cochrane Library from their inception to July 2023. The search strategies were ("Vitamin K"[MeSH Terms] OR "Vitamin K2"[MeSH Terms] OR "Vitamin K"[Title/Abstract] OR "vitamin k2"[Title/Abstract] OR "menaquinone"[Title/Abstract] OR "vitamin k intake"[Title/Abstract]) AND ("Bone Density"[MeSH Terms] OR "bone mineral density"[Title/Abstract] OR "body composition"[Title/Abstract]). We also browsed the reference lists

of original researches, reviews, and meta-analyses to avoid omitted studies. In addition, the search strategy of this meta-analysis and systematic review was not restricted to the articles' publication year.

Eligibility criteria

The studies were selected if they met the following inclusion criteria: original study with full text; RCTs; middle-aged and elderly participants (mean age ≥ 45 years); vitamin K supplement of any form and clear dosage; placebo, calcium, vitamin D, or blank control group; study focus on bone-related diseases or bone metabolism; and including at least one of the following outcomes: 1) BMD, including femoral neck BMD, lumbar spine BMD, total hip BMD, femoral Ward's triangle BMD, and ultra distal radius BMD (measured by dual-energy x-ray absorptiometry (DXA) in all RCTs); 2) total osteocalcin (tOC); 3) undercarboxylated osteocalcin (ucOC); 4) osteocalcin (OC); 5) ucOC to tOC ratio; 6) cOC to ucOC ratio; 7) NTx; 8) BAP; 9) PINP; and 10) S-25-OH-vitamin D.

The exclusion criteria were as follows: duplicate or non-full-text literature (including conference abstracts and preprint articles); non-RCTs; reviews; animal or cell experiments; special population groups, such as athletes; unrelated literature; and inappropriate age of study subjects, e.g. adolescents.

Data extraction

Two authors (CX, JG) independently extracted the following information from the selected studies: the first author, year of publication, country, study design, total sample size, mean age, sex, type of intervention, dose, duration, and population style. Moreover, the mean and SD of baseline and post-intervention changes in biomarkers and other relevant information were extracted. If the studies provided results for multiple time periods, the final outcomes were selected. If the studies had multiple intervention groups with different doses, we would combine different dose interventions. For studies in one control group consisting of two or more intervention groups, the general control group may be divided into two or more groups. ImageJ (National Institutes of Health, USA) was used to extract the data for some studies that did not provide specific data but instead presented graphs. Finally, any conflicts were resolved through discussion.

Quality assessment

All included studies were assessed by two authors according to the Cochrane risk assessment tool for bias recommended by the Cochrane Handbook.[28] The Cochrane risk assessment tool for bias consists of seven items: 1) random sequence generation (selection bias); 2) allocation concealment (selection bias); 3) blinding of participants and personnel (performance bias); 4) blinding of outcome assessment (detection bias); 5) incomplete outcome data (attrition bias); 6) selective reporting (reporting bias); and 7) other bias. The degree of bias was divided into low risk, high risk, and unclear risk.

Statistical analysis

Statistical analysis was completed by Stata 11.0 (StataCorp, USA). A p-value ≤ 0.05 was regarded as statistically significant. Weighted mean differences (WMDs) and 95% CIs were used when the units of the results were consistent, while standardized mean difference (SMD) was used when they were inconsistent. Data were analyzed using a random effects model, and I^2 static analysis was used to assess inter-study heterogeneity with low, medium, and high heterogeneity of 25%, 50%, and 75%, respectively.[29] A sensitivity analysis to evaluate the stability of the results was performed. Egger's test and funnel plots were used to determine publication bias, and the trim-and-fill method was used to correct for publication bias when it existed. In addition, we performed subgroup analyses of intervention type, dose, intervention duration, country, sex, health status, and BMD at different lumbar spine sites to identify sources of heterogeneity.

Results

Search results

The study inclusion process is shown in Figure 1. We retrieved 2,839 studies from three databases (PubMed, Web of Science, Cochrane). Seven RCTs were obtained from other sources. After removing the duplicated 678 studies, the titles and abstracts of the remaining 2,168 studies were screened. Then, 2,043 articles were excluded for various reasons, while 118 articles with full text were left. Of these, 108 articles were removed for non-RCTs, inappropriate results, irrelevant content, etc. Finally, 17 studies were included in this meta-analysis.[24,25,30–44]

Study characteristics and quality assessment

Table I summarizes the results of the study characteristics, and Figure 2 shows the risk of bias in the included studies. The 17 included studies contained a total of 4,800 study subjects; six studies had male and female participants.[31,32,34,36,37,41] Among these studies, there were five RCTs of vitamin K1 interventions,[32,36,37,39,41] 11 studies of vitamin K2 interventions,[24,25,30,31,33–35,38,42–44] and one study involving vitamin K1 and vitamin K2.[40] The intervention measures for these studies ranged from 9.4 μg/day to 100 mg/day, and the duration of the intervention ranged from two weeks to four years. The methods for generating random sequences and concealing random assignment schemes are described in detail in seven studies.[31,34,35,37,39,43,44] In addition, ten studies in the literature used blind methods for both participants and subjects. [30,32–35,37,39–41,44]

Effects of vitamin K supplementation on changes in bone mineral density

The effects of vitamin K supplementation on changes in lumbar spine BMD are shown in Figure 3. Vitamin K supplementation increased BMD of lumbar spine (WMD = 0.01 g/cm^2; 95% CI 0.00 to 0.03; I^2 = 92.1%; p = 0.035) (Figure 3a). However, the result showed that the effect of vitamin K on lumbar spine BMD became insignificant (WMD = 0.00 g/cm^2; 95% CI -0.01 to 0.01; I^2 = 80.4%; p = 0.574) (Figure 3b) when the study of Yuanyang et al[24] was removed based on the sensitivity analysis (Figure 3c). No significant effect of vitamin K was found on femoral neck BMD (WMD = 0.01 g/cm^2; 95% CI -0.00 to 0.02; I^2 = 81.4%; p = 0.245) (Figure 4a), femoral Ward's triangle BMD (WMD = 0.00 g/cm^2; 95% CI -0.02 to 0.02; I^2 = 0.0%; p = 0.906) (Figure 4b), total hip BMD (WMD = 0.01 g/cm^2; 95% CI -0.01 to 0.03; I^2 = 81.2%; p = 0.174) (Figure 4c), and ultra distal radius BMD (WMD = 0.00 g/cm^2; 95% CI -0.02 to 0.03; I^2 = 0.0%; p = 0.720) (Figure 4d).

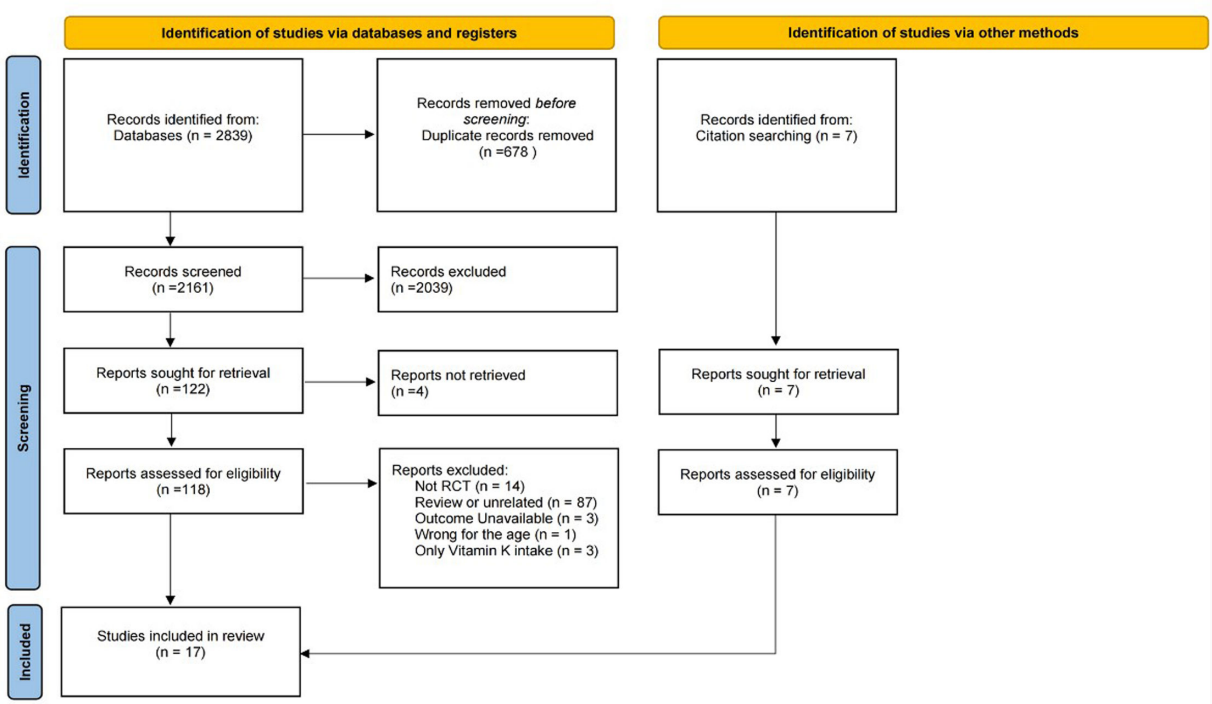

Fig. 1
Flowchart for the study screening process. RCT, randomized controlled trial.

Effects of vitamin K supplementation on changes in bone metabolism

As for the bone metabolism biomarkers, a significant increase in cOC after vitamin K supplementation was discovered by the pooled effect test (WMD = 2.87 ng/ml; 95% CI 0.90 to 4.84; I^2 = 92.8%; p = 0.004) (Figure 5a). Nine studies reported a significant reduction of ucOC in the vitamin K group (WMD = -2.32 ng/ml; 95% CI -3.32 to -1.32; I^2 = 97.2%; p = < 0.001) (Figure 5b).[30,33,36–38,42–44] Nine studies described no significant effect of vitamin K supplementation on the improvement in tOC (WMD = 1.13 ng/ml; 95% CI -0.12 to 2.39; I^2 = 93.8%; p = 0.076) (Figure 5c).[24,25,35,36,38,39,41,43,44] Furthermore, the pooled effect of vitamin K supplementation significantly increased the ratio of cOC to ucOC (WMD = 1.98; 95% CI 0.74 to 3.21; I^2 = 74.3%; p = 0.002) (Figure 5d) and decreased the ratio of ucOC to tOC (WMD = -0.21; 95% CI -0.41 to -0.01; I^2 = 77.0%; p = 0.043) (Figure 5e). No effect on NTx, BAP, and PINP by vitamin K supplementation was found (WMD = 0.19 nM; 95% CI -0.91 to 1.30; I^2 = 94.7%; p = 0.731; WMD = 0.61 μg/l; 95% CI -2.00 to 3.22; I^2 = 43.2%; p = 0.645; WMD = 10.08 μg/l; 95% CI -1.71 to 21.87; I^2 = 93.4%; p = 0.094) (Figures 5f to 5h).

In addition, the forest plots of the change in S-25-OH-vitamin D, serum vitamin K1, and MK-7 are shown in Supplementary Figures aa to ac. The result showed that vitamin K supplementation increased the serum MK-7 but had no effect on S-25-OH-vitamin D and vitamin K1.

Subgroup analyses

The results of the subgroup analysis of BMD are shown in Table II. Subgroups such as intervention type, dose, duration, country, sex, health status, and lumbar spine sites were explored in this meta-analysis. As an important fat-soluble vitamin, vitamin K is mainly divided into vitamin K1 and vitamin K2. In the subgroup supplemented with vitamin K2, a significant increase in lumbar spine BMD was observed (p = 0.028). As for intervention dose, the subgroup analysis revealed an increase in lumbar spine BMD in the subgroup with vitamin K supplementation > 1 mg/day (p = 0.008). The lumbar spine of humans has five segments; vitamin K was found to improve BMD at L2-L4 more significantly in subgroup analyses (p = 0.019). In addition to these, subgroup analyses showed that vitamin K improved the lumbar spine BMD in females (p = 0.028). However, no significant effects of vitamin K on femoral neck BMD, total hip BMD, ultra distal radius BMD, and femoral Ward's triangle BMD were revealed in the subgroup analysis. The results of these are shown in Table II and Supplementary Table i.

In the subgroup analysis of bone metabolism indicators, vitamin K supplementation increased the levels of cOC in a subgroup with vitamin K2 (p < 0.001), a subgroup with intervention duration > one year (p < 0.001), and a female subgroup (p < 0.001). In addition, vitamin K supplementation significantly reduced the levels of ucOC in subgroups of vitamin K1 (p = 0.003) and vitamin K2 (p = 0.004), subgroups of dose ≤ 1 mg/day (p = 0.002) and > 1 mg/day (p = 0.006), and subgroups of intervention duration ≤ one year (p = 0.007) and > one year (p = 0.030). The subgroup analyses of tOC showed that intervention dose of vitamin K > 1 mg/day increased the tOC. For NTx and BAP, no significant differences were found between the subgroups. Apart from these, vitamin K increased cOC to ucOC in sex-specific subgroups and decreased ucOC to tOC in intervention type, dose, country, sex, and health status subgroups. The results of these are shown in Table III and Supplementary Tables ii and iii.

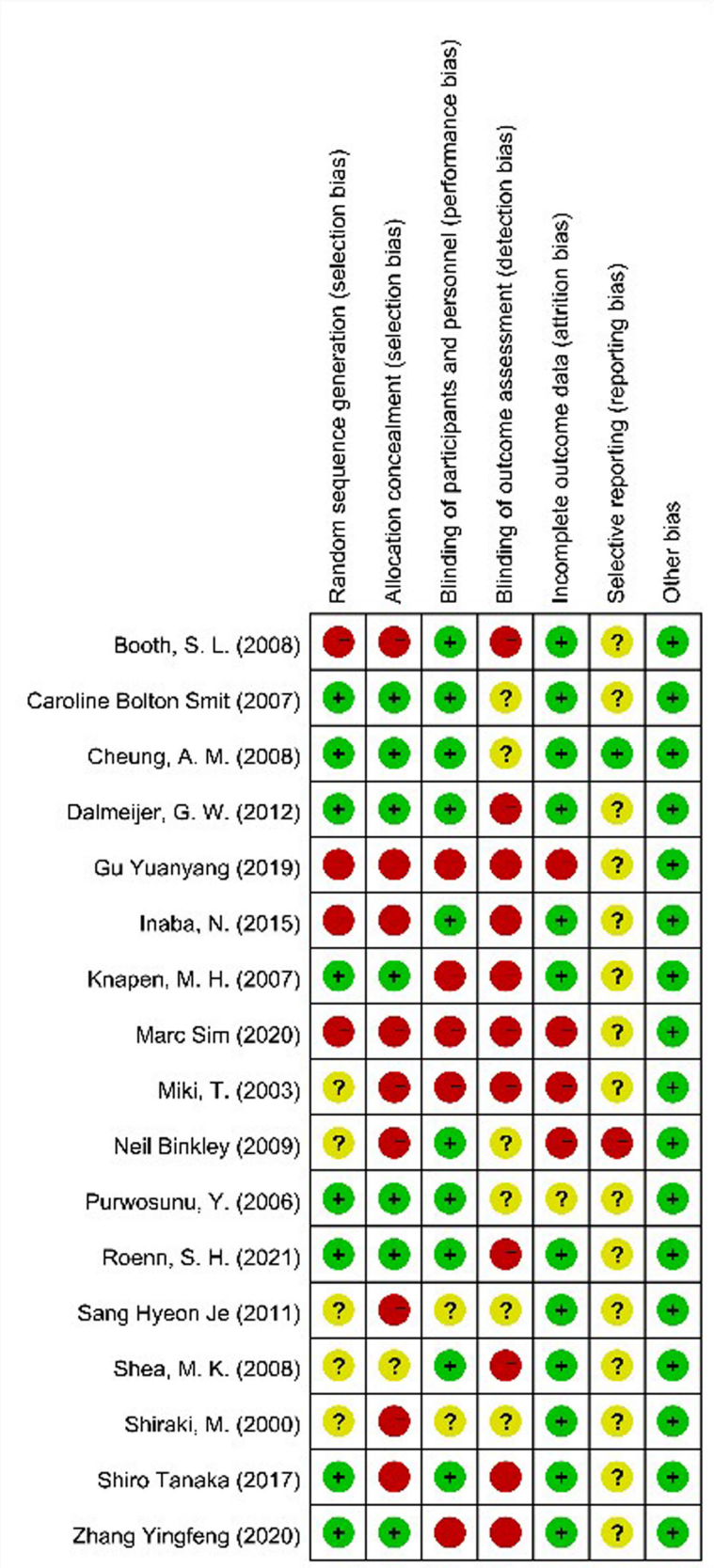

Fig. 2
Risk of bias summary.

Publication bias and sensitivity analysis

Egger's tests showed no publication bias, except for ucOC. They revealed a possible effect of publication bias only in the meta-analysis that calculated the effect of vitamin K supplementation on ucOC ($p = 0.001$). However, there was no indication of publication bias with the trim and fill method (no

Table I. Characteristics of 17 randomized controlled trials included in the meta-analysis.

Studies	Country	Health status	Sex	Mean age, yrs (SD)	Mean BMI, kg/m^2 (SD)	Duration	Intervention type (no. patients)	Control type (no. patients)	Dose of Vit K
Booth et al[32] (2008)*	USA	Healthy	F/M	68.41 (5.56)	N/A	3 yrs	Vit K1+ Ca + Vit D (229)	Ca + Vit D (223)	500 μg/day
Zhang et al[31] (2020)	China	Healthy	F/M	59.78 (6.60)	24.1 (3.3)	1 yr	Vit K2-1 (MK-7) (79), Vit K2-2 (MK-7) (74)	Placebo (61)	50 μg/day, 90 μg/day
Sim et al[36] (2020)†	Australia	Healthy	F/M	61.80 (9.90)	27.0 (3.9)	4 wks	Vit K1 (30), Vit K1 (30)	Blank control (30)	164.3 μg/day, 9.4 μg/day (low)
Shea et al[41] (2008)*	USA	Healthy	F/M	69.00 (6.00)	N/A	3 yrs	Vit K1+ Ca + Vit D (189)	Ca + Vit D (190)	500 μg/day
Inaba et al[33] (2015)‡	Japan	Healthy	F/M	47.00 (14.00)	21.8 (2.2)	3 mths	Vit K2 (MK-7) (58)	Placebo (57)	100 mg/day
Bolton-Smith et al[37] (2007)§	UK	Healthy	F	67.75 (5.46), 68.61 (5.96)	26.3 (3.5), 25.9 (3.5)	2 yrs	Vit K1 (54), Vit K1 + Ca + Vit D (49)	Placebo (56), Ca + Vit D (50)	200 μg/day, 200 μg/day
Tanaka et al[30] (2017)	Japan	Osteoporosis	F	75.30 (5.85)	23.3 (3.8)	2 yrs	Vit K2 + Risedronate (931)	Risedronate (n = 943)	45 mg/day
Je et al[38] (2011)	South Korea	N/A	F	67.60 (6.29)	N/A	6 mths	Vit K2 + Ca + Vit D (18)	Ca + Vit D (27)	45 mg/day
Yuanyang et al[24] (2019)	China	Osteoporosis	F	64.07 (9.63)	N/A	1 yr	Vit K2 (n = 70)	Blank control (n = 70)	45 mg/day
Shiraki et al[25] (2000)	Japan	Osteoporosis	F	67.20 (1.13)	N/A	2 yrs	Vit K2 + Ca (120)	Placebo + Ca (121)	100 mg/day
Binkley et al[40] (2009)	USA	Healthy	F	62.50 (0.68)	N/A	1 yr	Vit K1 + Ca + Vit D (126), Vit K2 (MK-4) + Ca + Vit D (126)	Placebo + Ca + Vit D (129)	1 mg/day, 45 mg/day
Cheung et al[39] (2008)	Canada	Osteopenia	F	59.05 (9.57)	26.2 (4.5)	4 yrs	Vit K1 + Ca + Vit D (n = 33)	Placebo + Ca + Vit D (40)	5 mg/day
Knapen et al[43] (2007)	Netherlands	Healthy	F	65.95 (0.46)	27.2 (0.4)	3 yrs/1 yr	Vit K2 (MK-4) (161)	Placebo (164)	45 mg/day
Purwosunu et al[44] (2006)	Indonesia	Osteoporosis	F	60.76 (5.25)	23.2 (3.9)	1 yr	Vit K2 + Ca (33)	Placebo + Ca (30)	45 mg/day
Miki et al[42] (2003)	Japan	Osteoporosis	F	75.80 (6.26)	N/A	2 wks	Vit K2 (MK-4) + Ca (10)	Ca (10)	45 mg/day
Dalmeijer et al[34] (2012)	Netherlands	Healthy	F/M	54.49 (2.96)	N/A	3 mths	Vit K2 (MK-7) (22), Vit K2 (MK-7) (18)	Placebo (20)	180 μg/day (low), 360 μg/day
Roenn et al[35] (2021)	Denmark	Osteopenia	F	67.26 (4.38)	N/A	3 yrs	Vit K2 (MK-7) + Ca + Vit D (62)	Placebo + Ca + Vit D (57)	375 μg/day

*The same study subjects were used in both studies, but they showed different indicators.
†The included participants did not mention bone-related diseases and were considered healthy by default.
‡There were two studies by this author, and only study 2 was listed here.
§There were four groups in this study, which have been divided into two studies.
N/A, not available (unable to consolidate or not provided).

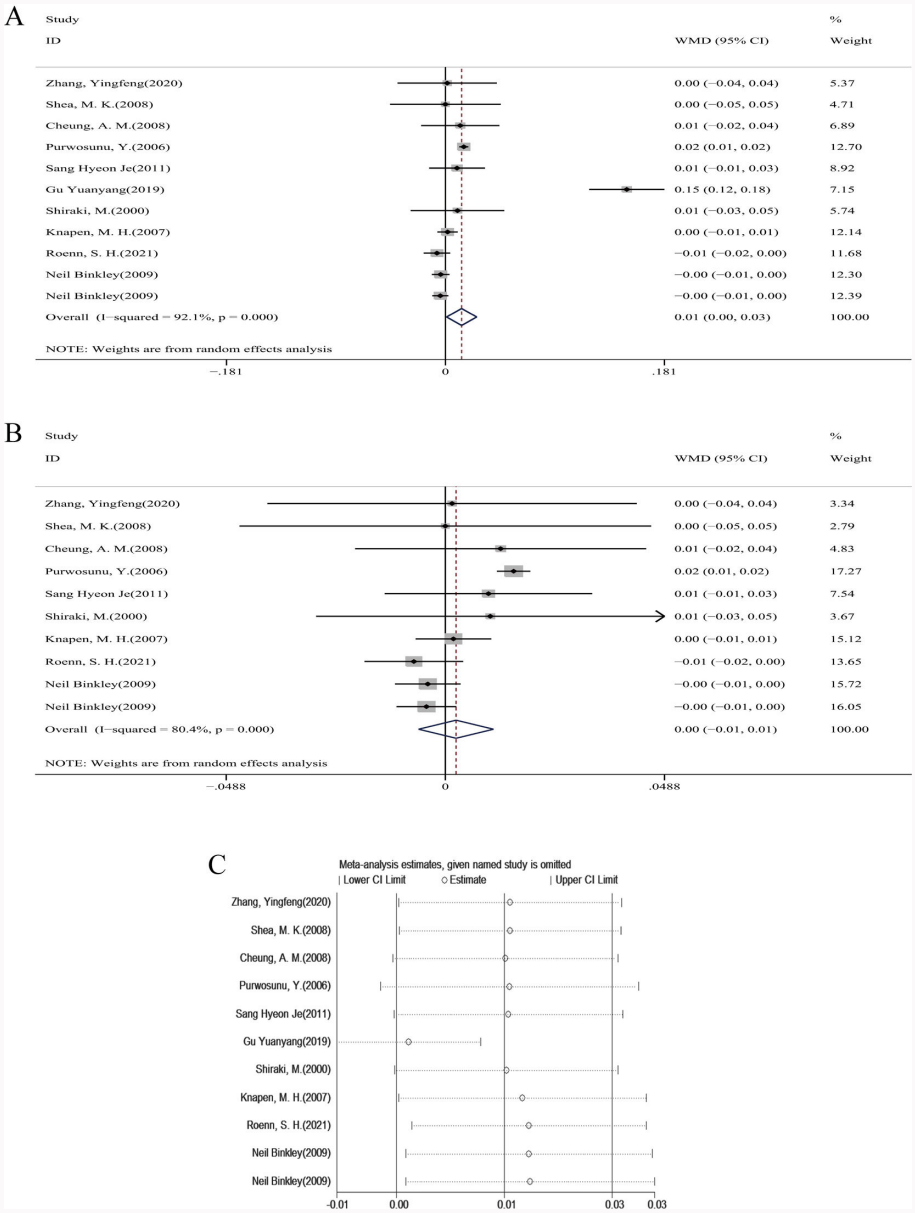

Fig. 3

Forest plots of a) the change in lumbar spine bone mineral density (BMD) and b) the change in lumbar spine BMD after removing the study by Yuanyang et al.[24] c) Sensitivity analysis of the change in lumbar spine BMD. WMD, weighted mean difference.

new studies added) (Supplementary Figures b to d). As for the sensitivity analysis, the results showed that when any of the 17 studies were removed, the points representing the statistical effects of the remaining studies were distributed around the vertical line of the overall statistical effect and within the 95% CI (Supplementary Figure e).

Discussion

The results of our meta-analysis indicated that vitamin K yielded improvements in lumbar spine BMD, but did not have a statistically significant effect on femoral neck BMD, total hip BMD, ultra distal radius BMD, or femoral Ward's triangle BMD based on pooled analysis. At the same time, vitamin K supplementation resulted in a decrease in ucOC and increased cOC levels, demonstrating favourable effects on bone metabolism. However, there was no discernible effect on other bone metabolism markers, such as tOC, NTx, BAP, or PINP, through their supplementation.

It is widely recognized that BMD serves as a crucial indicator of osteoporosis. In a recent study, it was demonstrated that supplementation with vitamin K led to an increase in lumbar spine BMD ($p = 0.035$). However, following a sensitivity analysis to exclude the study by Yuanyang et al,[24] no significant effect of vitamin K supplementation on lumbar spine BMD was observed. This suggests that the initial result may have been less stable. The Yuanyang et al[24] study was of poor quality, but it reported a significant increase in lumbar spine BMD with vitamin K supplementation. The potential for selection bias due to easy censoring in this study necessitates caution when assuming that vitamin K supplementation either maintains or increases lumbar spine BMD. However, it is worth mentioning that there were other studies with similar results.[17,26,45] The present data also indicated that vitamin K had

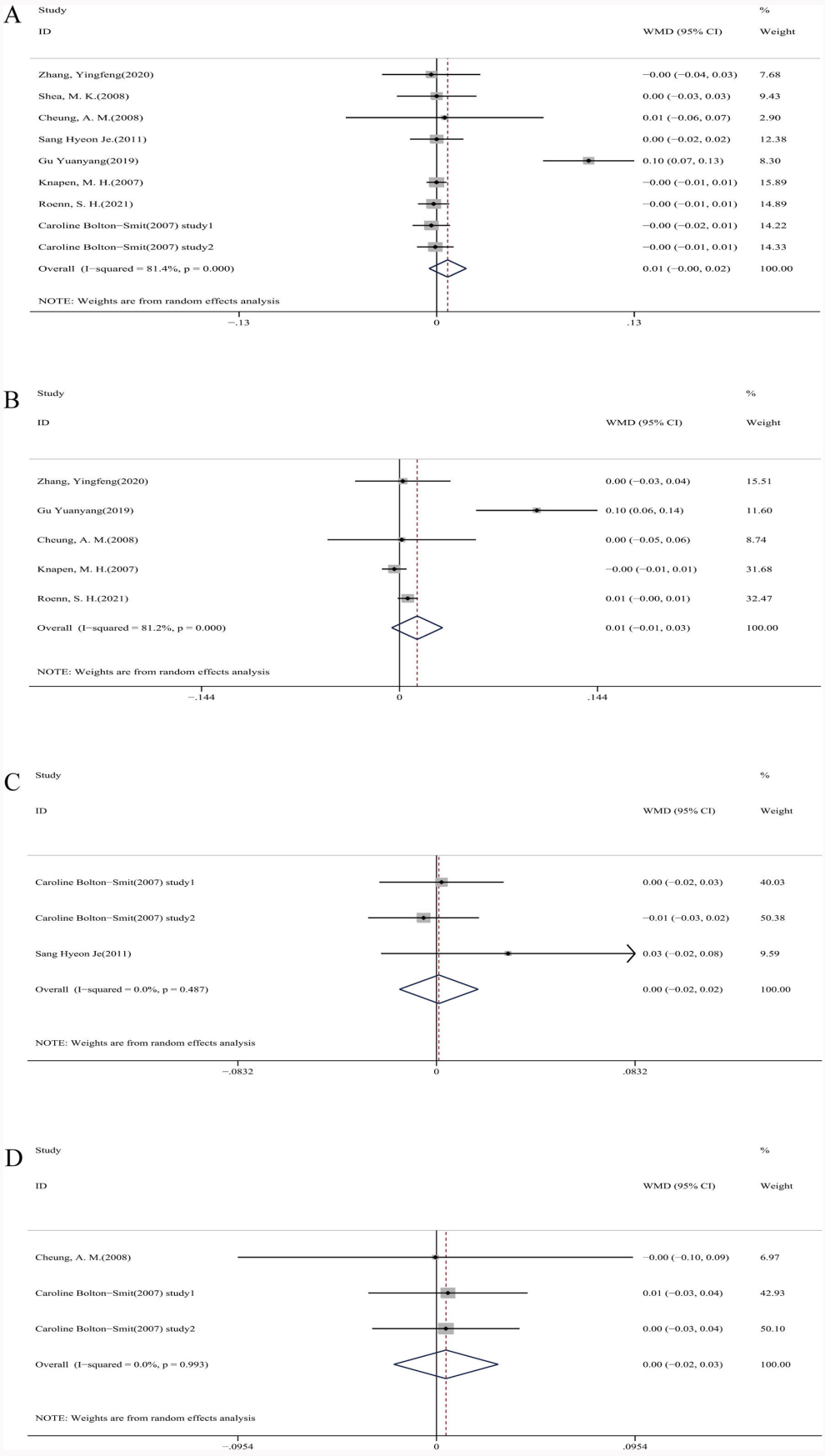

Fig. 4

Forest plots of the change in a) femoral neck bone mineral density (BMD); b) total hip BMD; c) femoral Ward's triangle BMD; and d) ultra distal radius BMD. WMD, weighted mean difference.

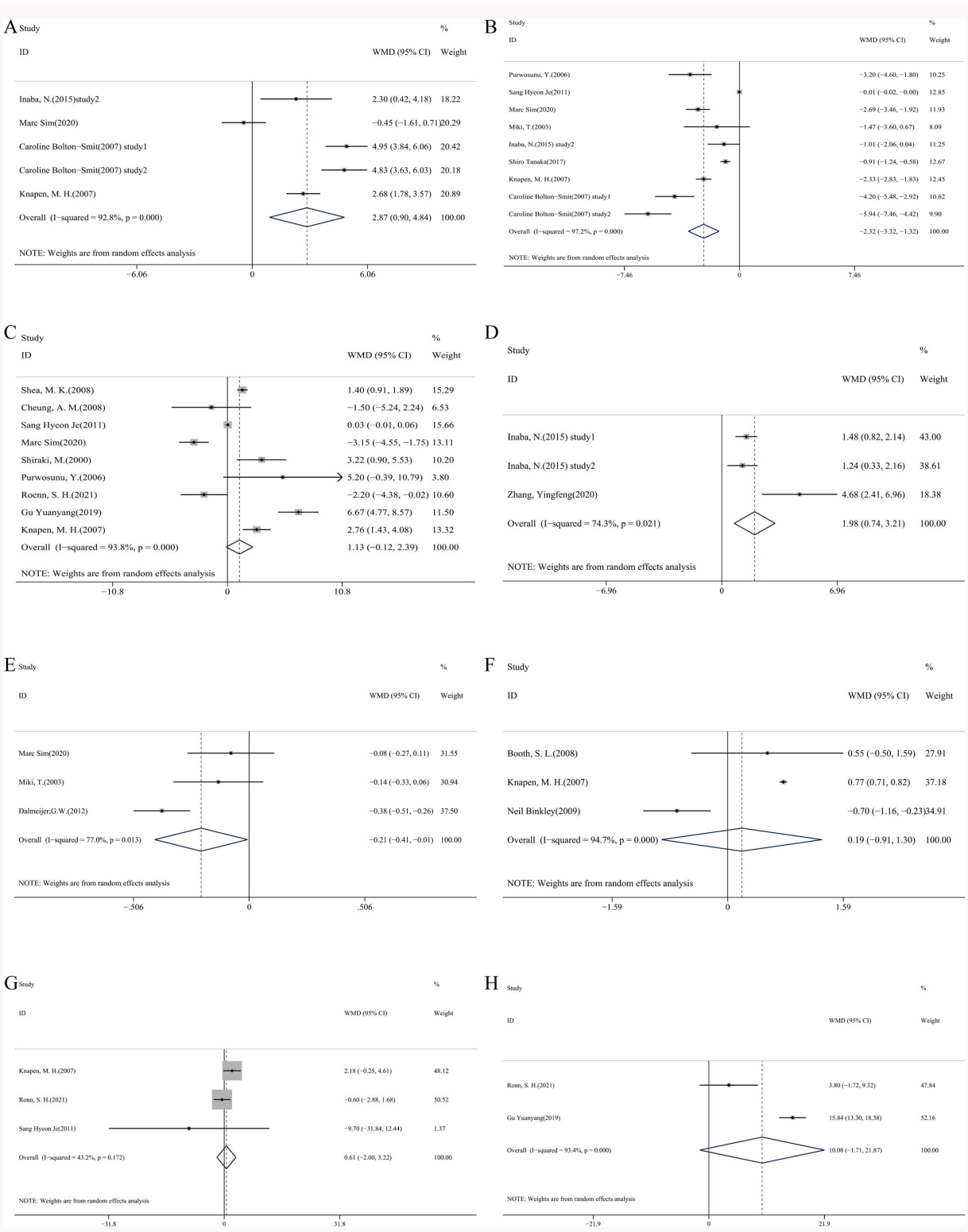

Fig. 5

Forest plots of the change in a) carboxylated osteocalcin (cOC); b) uncarboxylated osteocalcin (ucOC); c) total osteocalcin (tOC); d) cOC to ucOC; e) ucOC to tOC; f) cross-linked telopeptide of type 1 collagen (NTx); g) bone alkaline phosphatase (BAP); and h) procollagen I N-terminal propeptide (PINP).

no significant effect on femoral BMD, in line with the results of the systematic review by Salma et al,[46] although the meta-analysis conducted by Zhou et al[27] pointed out that vitamin K2 significantly increased the percentage of femoral BMD. The subjects recruited in the study by Zhou et al[27] were limited to females with osteoporosis. Additionally, when considering the results of total hip BMD, ultra distal radius BMD, and femoral Ward's triangle BMD, no significant improvements were found after vitamin K supplementation. Therefore, our meta-analysis did not find significant evidence of vitamin K supplementation improving BMD.

Table II. Subgroup analysis of the effects of vitamin K supplementation on femoral neck, lumbar spine, and total hip bone mineral density.

Subgroup	Femoral neck BMD (g/cm²)				Lumbar spine BMD (g/cm²)				Total hip BMD (g/cm²)			
	N	WMD (95% CI)	Heterogeneity		N	WMD (95% CI)	Heterogeneity		N	WMD (95% CI)	Heterogeneity	
			I^2	p-value			I^2	p-value			I^2	p-value
Intervention												
Vitamin K1	4	-0.00 (-0.01 to 0.01)	0.0%	0.657	3	-0.00 (-0.01 to 0.0)	0.0%	0.398	1	0.00 (-0.05 to 0.06)	N/A†	0.954
Vitamin K2	6	0.02 (-0.00 to 0.04)	88.2%	0.100	9	0.02 (0.00 to 0.03)	93.1%	0.028	5	0.01 (-0.01 to 0.03)	81.2%	0.173
Dose, mg/day												
≤ 1	6	-0.00 (-0.01 to 0.00)	0.0%	0.671	5	-0.00 (-0.01 to 0.00)	0.0%	0.132	3	0.01 (-0.00 to 0.01)	0.0%	0.113
> 1	4	0.03 (-0.01 to 0.06)	92.7%	0.175	7	0.02 (0.01 to 0.04)	94.4%	0.008	3	0.03 (-0.03 to 0.10)	90.2%	0.348
Duration, yrs												
≤ 1	4	0.03 (-0.02 to 0.08)	90.9%	0.2290	7	0.02 (0.00 to 0.04)	94.9%	0.020	3	0.03 (-0.03 to 0.10)	84.9%	0.275
> 1	6	-0.00 (-0.01 to 0.00)	0.0%	0.600	5	-0.00 (-0.01 to 0.01)	0.0%	0.859	3	0.00 (-0.01 to 0.01)	26.7%	0.664
Country												
Asia	4	0.03 (-0.02 to 0.08)	90.9%	0.229	6	0.03 (-0.01 to 0.07)	93.1%	0.103	3	0.03 (-0.03 to 0.10)	84.9%	0.275
Other continents	6	-0.00 (-0.01 to 0.00)	0.0%	0.660	6	-0.00 (-0.01 to 0.0)	0.0%	0.148	3	0.00 (-0.01 to 0.01)	26.7%	0.664
Sex												
Female	7	0.01 (-0.0 to 0.02)	86.0%	0.188	9	0.01 (0.00 to 0.03)	93.7%	0.028	4	0.02 (-0.01 to 0.04)	85.9%	0.150
Female and male	3	0.00 (-0.01 to 0.02)	0.0%	0.630	3	0.00 (-0.03 to 0.03)	0.0%	0.942	2	0.00 (-0.03 to 0.03)	0.0%	0.866
Position												
L1-L4					4	-0.00 (-0.01 to 0.00)	0.0%	0.062				
L2-L4					8	0.02 (0.00 to 0.05)	91.6%	0.019				
Health status												
Healthy									3	-0.00 (-0.01 to 0.01)	0.0%	0.460
Unhealthy*									3	0.03 (-0.02 to 0.09)	88.2%	0.251

*Participants with osteoporosis or osteopenia.
†Only one document included, not shown.
BMD, bone mineral density; N/A, not applicable; WMD, weighted mean difference.

Next, we tried to further analyze the effects of vitamin K supplementation on bone markers. Osteocalcin, also referred to as bone γ-carboxyglutamate (Gla) protein or BGP, is a vitamin K-dependent protein secreted by osteoblasts.[47,48] It contains three glutamate residues, and vitamin K assists in γ-carboxylation of these glutamate residues and the conversion of ucOC to cOC, which possesses the ability to bind to calcium ions in hydroxyapatite, thereby promoting BMD.[47,49] In this meta-analysis, the total effect of vitamin K increased cOC, contrary to the results of Ma et al[50] and Lombardi et al[51] due to the differences of the subjects included. As for the assessment of ucOC, the significant reduction in ucOC by vitamin K was consistent with many previous studies.[17,21,51,52] This suggests that vitamin K supplementation promotes the γ-carboxylation of OC, leading to higher levels of cOC and lower levels of ucOC. The pooled effect of vitamin K

Table III. Subgroup analysis of the effects of vitamin K supplementation on total osteocalcin, uncarboxylated osteocalcin, and carboxylated osteocalcin.

Subgroup	Total OC, ng/ml				ucOC, ng/ml				cOC, ng/ml			
	N	WMD (95% CI)	Heterogeneity		N	WMD (95% CI)	Heterogeneity		N	WMD (95% CI)	Heterogeneity	
			I^2	p-value			I^2	p-value			I^2	p-value
Intervention												
Vitamin K1	4	-0.91 (-3.20 to 1.39)	93.5%	0.439	4	-3.25 (-5.41 to -1.08)	95.1%	0.003	4	2.24 (-0.76 to 5.23)	96.6%	0.144
Vitamin K2	6	2.37 (-0.02 to 4.76)	93.6%	0.052	6	-1.39 (-2.43 to -0.45)	96.2%	0.004	2	2.61 (1.80 to 3.41)	0.0%	< 0.001
Dose, mg/day												
≤ 1	4	-1.10 (-3.34 to 1.15)	94.2%	0.338	5	-2.78 (-4.52 to -1.04)	93.8%	0.002	5	2.25 (-0.28 to 4.78)	95.5%	0.082
> 1	6	2.64 (0.14 to 5.15)	93.3%	0.039	5	-1.47 (-2.53 to -0.42)	97.0%	0.006	1	2.68 (1.78 to 3.57)	N/A*	< 0.001
Duration, yrs												
≤ 1	6	1.29 (-0.62 to 3.2)	94.4%	0.186	7	-1.56 (-2.68 to -0.43)	96.1%	0.007	4	1.00 (-0.77 to 2.78)	89.7%	0.269
> 1	4	0.45 (-1.70 to 2.60)	79.7%	0.682	3	-3.62 (-6.88 to -0.36)	96.7%	0.030	2	4.89 (4.08 to 5.71)	0.0%	< 0.001
Country												
Asia	4	3.59 (-0.38 to 7.57)	81.1%	0.076	5	-1.08 (-1.88 to -0.27)	92.6%	0.009	1	2.30 (0.42 to 4.18)	N/A*	0.016
Other continents	6	-0.44 (-2.24 to 1.36)	92.4%	0.630	5	-3.00 (-4.42 to 1.58)	93.5%	< 0.001	5	2.32 (0.08 to 4.56)	95.6%	0.042
Sex												
Female	7	1.91 (-0.28 to 4.10)	92.3%	0.087	7	-2.45 (-3.57 to -1.33)	94.0%	< 0.001	3	4.12 (2.55 to 5.68)	84.6%	< 0.001
Female and male	3	-0.79 (-3.35 to 1.77)	95.6%	0.545	3	-1.39 (-2.83 to 0.05)	89.4%	0.058	3	0.28 (-1.09 to 1.65)	71.0%	0.688

*Only one document included, not shown.
N/A, not applicable.

supplementation on the ratio of cOC to ucOC also confirmed our speculation. Although some studies reported that vitamin K increased the level of tOC, no significant correlation was found between vitamin K supplementation and tOC in this study.[17,27] Our findings suggest that vitamin K supplementation primarily promotes carboxylation of OC rather than increasing the total amount of it. Our analysis also included additional bone metabolism markers that were not extensively covered in previous studies.[17,26,27,46,50] The meta-analysis revealed no significant effect of vitamin K on NTx, BAP, or PINP, which is inconsistent with previous studies.[53,54] One possible explanation for this lack of statistical significance may be the limited number of included studies. Another possible reason is that the control group primarily used calcium and vitamin D, and their known effect on bone may have obscured any potential impact of vitamin K on bone markers. These results further indicated that vitamin K supplementation primarily affects bone health through carboxylation of OC, with minimal impact on other bone metabolism markers. The fact that only OCN-related biomarkers changed suggests that we may need to consider the combined use of other bone nutrients. Further research is needed to fully understand the mechanisms by which vitamin K affects bone metabolism.

Vitamins K1 and K2 are the two main forms, which come from different food sources. In a subgroup analysis, it was found that vitamin K2 was more effective than vitamin K1 in improving lumbar spine BMD and osteocalcin in middle-aged and elderly individuals. Furthermore, our research indicated that vitamin K intervention had a more significant impact on human serum vitamin K2 compared to vitamin K1, possibly due to the long half-life of vitamin K2. One study also demonstrated that vitamin K1 returned to baseline levels after eight hours of supplementation, while significant amounts of vitamin K2 were still present.[55] Another possible reason for the greater efficacy of vitamin K2 is believed to be the side chain, which triggers an inhibitory effect on bone loss, a feature not present in vitamin K1.[56] Additionally, vitamin K supplementation was shown to have a notable effect on women with osteoporosis, indicating that this subgroup may benefit significantly from such interventions. Postmenopausal

women have a higher risk of osteoporosis compared to men due to the declining oestrogen levels and accelerated bone loss, resulting in decreased bone mass and changes in bone structure. The individuals in our study mainly comprised middle-aged and older adults, with a majority of women being postmenopausal. This factor could explain the significant effect of vitamin K supplementation observed in women in our study. In the subgroup analysis, a high dose of vitamin K had a significant effect on lumbar spine BMD, as well as on tOC and cOC. A study by Shiraki and Itabashi[57] indicated that a six-month vitamin K intervention resulted in improved osteocalcin carboxylation. However, the results of this study suggest that a longer duration of intervention may be necessary to observe a significant effect, emphasizing the need for further exploration of the optimal duration of intervention.

Compared to the previous studies, our study has many advantages. The inclusion of five indicators of BMD and eight bone metabolism indicators allowed for a comprehensive assessment of the effect of vitamin K on BMD and bone metabolism in middle-aged and elderly individuals. The detailed subgroup analysis provided substantial evidence for exploring heterogeneity within the data.

Recent research indicates that dietary patterns significantly impact osteoporosis prevention and fracture recovery.[58] Vitamin D3 supplementation can help to prevent distal radius comminuted fractures (DRFs) caused by vitamin D deficiency.[59] Based on our research findings, we would recommend enhancing public health campaigns to increase awareness regarding the significance of vitamin K2. In addition, we advise older adults, especially postmenopausal women, to consider the proper use of vitamin K supplements or to boost their consumption of green leafy vegetables and fermented foods. Lastly, we propose the development of personalized nutrition plans to optimize nutrient supplementation.

There were, however, some limitations to this meta-analysis and systematic review. Some indicators, such as PINP and NTx, were only present in a limited number of studies. Additionally, data on means and SDs were sometimes only available in graphical format, potentially introducing statistical bias. In the studies we included, we focused solely on osteoporosis and osteopenia, excluding other bone-related diseases such as osteoarthritis. This may limit our understanding of the effects of vitamin K on BMD and bone metabolism markers. Nevertheless, existing research indicates that ucOC (undercarboxylated osteocalcin) is associated with osteoarthritis, suggesting that vitamin K may also play a role in the bone metabolism process of osteoarthritis.[47] Furthermore, some studies involved the combination of vitamin K with other medications (calcium or vitamin D), which could have magnified the effects attributed to vitamin K. Future research should aim to provide more insights into the influence of vitamin K in combination with other compounds on BMD and bone metabolic biomarkers. Moreover, due to constraints in population intervention studies, in-depth discussions on the underlying mechanisms were limited. Therefore, further investigations utilizing animal models and cell experiments are warranted and will be a focal point of our future research endeavours. Despite these limitations, this study serves as a valuable resource for understanding the potential benefits of vitamin K on bone health.

The results of this meta-analysis and systematic review emphasize the positive effects of vitamin K, particularly vitamin K2, in maintaining or enhancing lumbar spine BMD in middle-aged and elderly individuals. These effects are largely attributed to the increased conversion of ucOC to cOC. Based on our research, future endeavours should focus on delving into the mechanisms of vitamin K, formulating dietary guidelines, promoting public health initiatives, designing personalized nutrition plans, and exploring the synergistic effects of nutrients. These endeavours seek to advance our understanding of the impact of dietary nutrition on bone health and ultimately improve the quality of life for middle-aged and elderly individuals.

Supplementary material

Tables and figures providing additional data and analyses to support the findings presented in this article, including subgroup analysis of the effects of vitamin K supplementation on ultra distal radius bone mineral density (BMD), femoral Ward BMD, cOC: ucOC, ucOC: tOC, NTx, and BAP; forest plots, publication bias tests; trim-and-fill method for the pooled effect of ucOC; and sensitivity analysis.

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Data sharing

The datasets generated and analyzed in the current study are not publicly available due to data protection regulations. Access to data is limited to the researchers who have obtained permission for data processing. Further inquiries can be made to the corresponding author.

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