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REVIEW ARTICLE

Effect of vitamin K on bone mineral density and fractures in adults: an updated systematic review and meta-analysis of randomised controlled trials

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Abstract

Summary Vitamin K may affect bone mineral density and fracture incidence. Since publication of a previous systematic review the integrity of some of the previous evidence has been questioned and further trials have been published. Therefore an update to the systematic review was required.

Introduction This systematic review was designed to assess the effectiveness of oral vitamin K supplementation for increasing bone mineral density and reducing fractures in adults.

Methods MEDLINE, EMBASE, CENTRAL, CINAHL, clinicaltrials.gov, and WHO-ICTRP were searched for eligible trials. Randomised controlled trials assessing oral vitamin K supplementation that assessed bone mineral density or fractures in adult populations were included. A total of 36 studies were identified. Two independent reviewers extracted data using a piloted extraction form.

Results For post-menopausal or osteoporotic patients, meta-analysis showed that the odds of any clinical fracture were lower for vitamin K compared to controls (OR, 0.72, 95%CI 0.55 to 0.95). Restricting the analysis to low risk of bias trials reduced the OR to 0.76 (95%CI, 0.58 to 1.01). There was no difference in vertebral fractures between the groups (OR 0.96, 95%CI 0.83 to 1.11). In the bone mineral density meta-analysis, percentage change from baseline at the lumbar spine was higher at 1 year (MD 0.93, 95%, CI − 0.02 to 1.89) and 2 years (MD 1.63%, 95%CI 0.10 to 3.16) for vitamin K compared to controls; however, removing trials at high risk of bias tended to result in smaller differences that were not statistically significant. At 6 months, it was higher in the hip (MD 0.42%, 95%CI 0.01 to 0.83) and femur (MD 0.29%, 95%CI 0.17 to 0.42). There was no significant difference at other anatomical sites.

Conclusions For post-menopausal or osteoporotic patients, there is no evidence that vitamin K affects bone mineral density or vertebral fractures; it may reduce clinical fractures; however, the evidence is insufficient to confirm this. There are too few trials to draw conclusions for other patient groups.

Keywords Bone health · Bone mineral density · Fracture · Osteoporosis · Systematic review · Vitamin K

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Introduction

Rationale

The present study is an update of a previous systematic review of vitamin K supplementation and the prevention of fractures published in 2006 [1]. The original analysis identified 13 trials with data on bone loss and seven with data on fractures. Eleven of these trials had used nutritional supplements of menaquinone-4 (MK-4), a member of the vitamin K2 family, whilst two trials had used phylloquinone (vitamin K1). At that time, all the trials with fracture outcomes had been undertaken in Japan with MK-4 supplementation in patients with pre-existing osteoporosis or in patients with diseases or treatments known to predispose to osteoporosis. An important incentive for us to update our systematic review was that in 2016 Bolland and colleagues conducted a review and statistical analysis of 33 RCTs (identified as originating from a group led by Yoshihiro Sato) which raised serious concerns regarding their integrity and validity [2, 3]. A number of the trials from the 2006 systematic review were identified as being problematic in this review; a correction was issued for the systematic review [2]. A retraction notice confirmed that Sato had fabricated trial data [4]. Another reason to carry out a new meta-analysis is that more RCTs have been published since our original analysis, in differing populations.

The central rationale for vitamin K supplementation as a potential treatment for the prevention of bone loss is centred on knowledge of the synthesis and functions of specific vitamin K-dependent proteins (also known as Gla proteins) within the cartilage and bone [5, 6]. The major bone Gla protein is osteocalcin (OC) which is synthesised by bone-forming osteoblasts with serum concentrations of OC correlating with the rate of bone formation [7]. Vitamin K is required for the posttranslational gamma-glutamyl carboxylation of OC and this step is responsive to dietary vitamin K depletion, repletion and supplementation. Further observational evidence suggested that lower concentrations of undercarboxylated osteocalcin (ucOC), expressed as a fraction of total OC, are associated with higher BMD and reduced hip fracture risk. [8–12]. It was therefore anticipated that reducing the fraction of ucOC by vitamin K supplementation might slow the rate of age-related bone loss and because a low BMD is associated with increased fracture risk, [13] might offer a treatment option for osteoporosis prevention. A recent systematic review of observational studies found that increased dietary intake of vitamin K may reduce the risk of fractures [14]. Vitamin K comprises a family of different molecular forms, a single form synthesised by plants (vitamin K1), and multiple forms mainly synthesised by bacteria (vitamins K2). The forms of vitamin K used in all RCTs to date are either vitamin K1 (the major dietary source) or two members of the vitamin K2 series, menaquinone-4 (MK-4) and menaquinone-7 (MK-7). MK-4 is unique in not being of bacterial origin but is able to be synthesised from dietary vitamin K1 within the body.

In the light of evidence presented above that the data from some trials used for the previous systematic review are unreliable [3] and new vitamin K trials have been published in the interim, we considered that an updated systematic review is required [15]. We have also expanded this systematic review to include bone mineral density (BMD) as an outcome measure in the meta-analysis.

Objectives

The objective of the study is to assess the effectiveness of oral vitamin K supplementation in increasing BMD and reducing fractures in adults.

Methods

Protocol

A protocol for this systematic review was prospectively registered on PROSPERO (CRD42018087492).

Eligibility criteria

Studies were eligible for inclusion if they fulfilled the below criteria:

(1) Population: adults (defined as over 18 years of age)
(2) Intervention: oral vitamin K supplement of any form or dosage administered for at least 6 months (min 25 weeks)
(3) Control: no treatment, treatment as usual, placebo, calcium, vitamin D, hormone replacement therapies, bisphosphonates
(4) Outcomes: any fracture outcome and/or BMD after 6 months
(5) Study design: randomised controlled trial

Exclusion criteria

Studies that have been questioned with respect to their scientific integrity were excluded. The exclusion was applied to any articles published by Yoshihiro Sato or any of his known collaborators, irrespective of retraction status. This was done as serious concerns about the integrity and validity of the results have been raised [3, 16, 17].

Literature search

The following electronic databases were searched: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, CINAHL, clinicaltrials.gov, WHO-ICTRP up till the 22nd

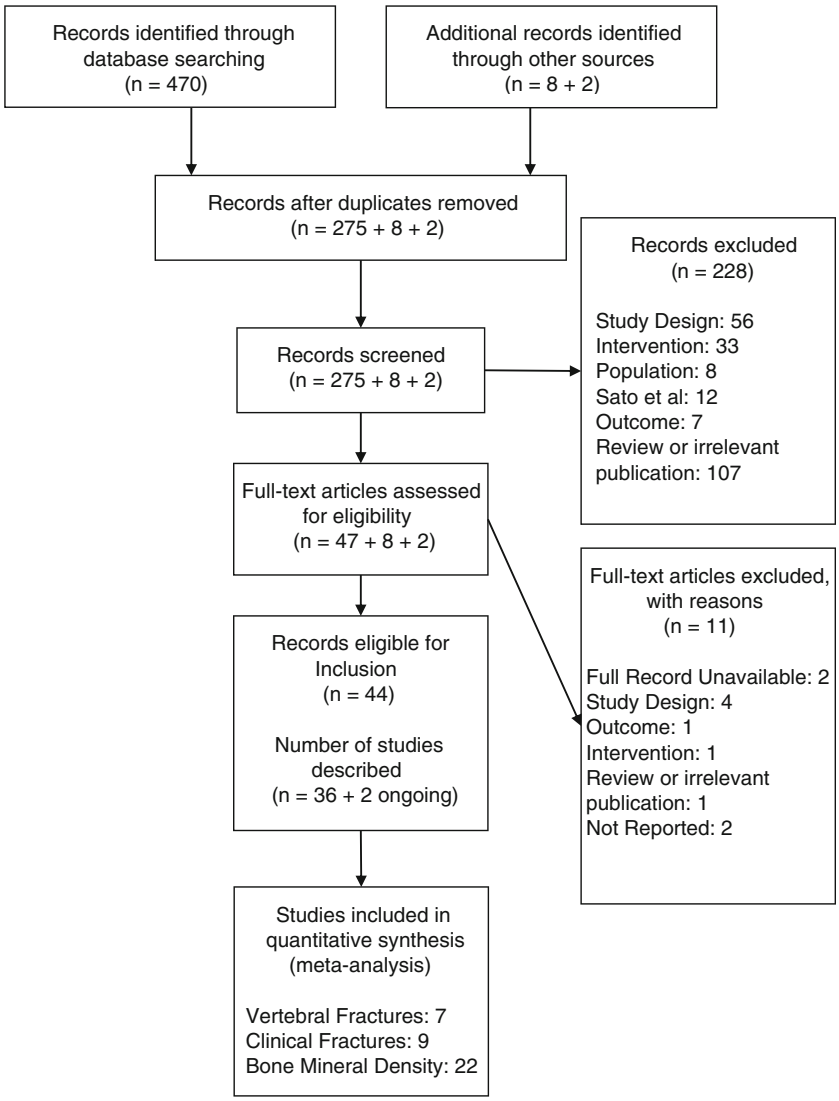


Fig. 1 A PRISMA flow diagram of study selection

January 2018. Searches relevant to fractures, BMD, vitamin K and randomised controlled trials were made. Hand searching of references within records was undertaken to identify further eligible trials. The search strategy can be found in Supplement 1.

Study selection

Records identified from searches were de-duplicated and the titles and abstracts were independently screened for inclusion by two authors; a decision on inclusion was reached through discussion. Full-text records were collated for the remaining articles and screened by the two authors, with any disagreements resolved by discussion.

Data collection

Data extraction was undertaken on the included studies independently by two authors. A piloted data extraction form, developed from the Cochrane Data Extraction and Assessment Template, was used to collect the information. Data reported only in graphical form were extracted using the Digitise package in R [18].

For each trial, the following data were collected: (i) participant characteristics (age, presence or severity of disease); (ii) intervention information (vitamin K form, frequency, dose); (iii) study design and conduct information (funding, ethical approval, protocols and registry entries, eligibility criteria) and (iv) fracture and BMD outcomes.

Percentage change in BMD at 6 months, 1 year and 2 years at the lumbar spine, femur, radius and hip; total clinical fractures; total vertebral fractures and total hip fractures were the outcomes of interest.

The Cochrane risk of bias tool was used to assess studies as having a high or low risk of bias [19]. Two authors independently assessed each study and agreed a final classification through discussion. Studies that presented an unclear risk of

Table 1 Study characteristics of included studies

Author, year	Population	Country	Randomised (*n*)		Intervention (type, dose)	Control	Follow-up (months)	Age, (years [SD])	
			Control	Vitamin K				Control	Vitamin K
Binkley 2009 [27]	Postmenopausal, female	America	129	126/126	Ca, 315 mg VD, 200 IU K1, 1 mg/MK, 4–45 mg Matched placebo	Ca, 315 mg VD, 200 IU Matched placebos	1 year	NR	NR
Bolton-Smith 2007 [26]	Healthy, female, > 60 years	UK	123 (61 + 62)	121 (60 + 61)	K1, 200 μg K1, 200 μg VD, 10 μg Ca, 1000 mg	Placebo VD, 10 μg Ca, 1000 mg	2 years	68.6 (67.7)	67.8 (5.15)
Booth et al. 2008 [25]	Healthy, postmenopausal females and males between 60 and 80 years	America	236	238	VD, 10 μg Ca, 600 mg K1, 500 μg	VD, 10 μg Ca, 600 mg	3 years	68.4 (6)	68.4 (6)
Braam 2003 (a) [29]	Healthy, postmenopausal, female	The Netherlands	122 (61 + 61)	66	Ca, 500 mg Zn, 10 mg Mag, 150 mg VD, 8 μg K1, 1 mg	Ca, 500 mg Zn, 10 mg Mag, 150 mg VD, 8 μg Placebo	3 years	55.1 (2.9)	55.3 (2.8)
Braam 2003 (b) [28]	Female endurance athletes	North Europe	56	59	K1, 10 mg	Placebo	2 years	NR	NR
Cheung et al. 2008 [30]	Postmenopausal, osteopenic, female	Canada	223	217	VD, 800 IU Ca, 1500 mg K1, 5 mg	VD, 800 IU Ca, 1500 mg Placebo	2 years (ext to 4)	59.2	58.9
Emaus et al. 2010 [31]	Healthy, postmenopausal, female	Norway	167	167	MK-7 capsule, 360 μg	Placebo capsule	1 year	54.2 (2.5)	54.7 (2.5)
Forli et al. 2010 [32]	Transplant patients	Norway	48	46	VD, 10–20 μg Ca, 1000 mg MK-7, 180 μg	VD, 10–20 μg Ca, 1000 mg	1 year	NR	NR
Gleeson 2004 (abstract only) [34]	Primary biliary cirrhosis	UK	25	22	K2 (NR), 2 mg Ca, 1000 mg VD, 20 μg	Ca, 1000 mg VD, 20 μg Placebo	1 year	63 (11)	
Hampson (ongoing) [65]									
Hirao et al. 2008 [35]	Healthy postmenopausal female	Japan	26	22	Alendronate, 5 mg MK-4, 45 mg	Alendronate, 5 mg	1 year	69.8 (8.7)	67.0 (6.6)
Holden et al. (ongoing) [64]									
Hozuki et al. 2010 [36]	Patients with neuromuscular disorders	Japan	8	8	Risedronate, 2.5 mg corticosteroids MK-4, 45 mg	Risedronate, 2.5 mg corticosteroids	1 year	54.7 (5.4)	53.6 (5.6)
Inoue et al. 2009 [38]	Postmenopausal, female, osteoporosis	Japan	2193	2185	Ca, 1.2 g/3 g MK-4, 45 mg	Ca, 1.2 g/3 g	4 years	69.6 (8.25)	69.6 (8.32)

Table 1 (continued)

Author, year	Population	Country	Randomised (*n*)		Intervention (type, dose)	Control	Follow-up (months)	Age, (years [SD])	
			Control	Vitamin K				Control	Vitamin K
Inoue et al. 2014 [37]	Patients with IgA nephropathy	Japan	6	4	MK-4, 45 mg Calcitriol, 0.5 μg	Calcitriol, 0.5 μg	6 months	25.4 (5.9)	29.3 (4.2)
Ishida and Kawai 2004 [39]	Postmenopausal, female, osteoporosis	Japan	66	66	MK-4, 45 mg	Nothing	2 years	68 (8)	68 (11)
Iwamoto et al. 1999 [40]	Postmenopausal, female	Japan	19	17	MK-4, 45 mg	Nothing	1 year	53.6 (3.7)	52.6 (6.4)
Je et al. 2011 [41]	Postmenopausal, female	Korea	40	38	VD, 400 IU Ca, 630 mg MK-4, 45 mg	VD, 400 IU Ca, 630 mg	6 months	67.6 (6.2)	68.1 (6.3)
Jiang et al. 2014 [42]	Postmenopausal, female	China	105	108	Alfacalcidol, 0.5 μg Ca, 500 mg MK-4, 45 mg	Alfacalcidol, 0.5 μg Ca, 500 mg	1 year	64.2 (6.3)	64.6 (6.1)
Jokar et al. 2016 [43]	Postmenopausal, female, osteoporosis	Iran	23	24	Alendronate, 70 mg Ca, 500 mg VD, 200 IU K1, 10 mg	Alendronate, 70 mg Ca, 500 mg VD, 200 IU	1 year	59.0 (6.3)	59.0 (6.3)
Kanellakis/Moschonis et al. 2011/12 [45, 50]	Healthy, postmenopausal, female	Greece	65	50	K1, 100 μg Ca, 800 mg VD, 10 μg Ca, 800 mg VD, 10 μg MK-7, 100 μg	Ca, 800 mg VD, 10 μg	1 year	62.44 (5.93)	61.43 (5.88)
Kasukawa et al. 2014 [46]	Postmenopausal, female, osteoporosis	Japan	50	51	Risedronate, 17.5 mg (week) MK-4, 45 mg	Risedronate, 17.5 mg (week)	1 year	74.0 (6.9)	75.4 (5.7)
Knapen et al. 2013 [47]	Healthy, postmenopausal, female	The Netherlands	124	120	MK-7, 180 μg	Placebo	3 years	59 (3)	60 (4)
Knapen et al. 2007 [48]	Healthy, postmenopausal, female	The Netherlands	164	161	MK-4, 45 mg	Placebo	3 years	66.0 (6.4)	65.9 (5.1)
Koitaya et al. 2014 [49]	Postmenopausal women, female	Japan	24	24	MK-4, 1.5 mg	Placebo	1 year	58.5 (3.7)	58.3 (4.0)
Nishiguchi 2001 [51]	Female, primary biliary cirrhosis	Japan	15	15	MK-4, 45 mg	Nothing	2 years	55 (7)	56 (8)
O'Connor et al. 2014 [52]	Patients with Crohn's in remission	Ireland	43	43	VD, 10 μg Ca, 500 mg K1, 1 mg	VD, 10 μg Ca, 500 mg Placebo	1 year	40.7 (10.5)	42.0 (10.0)
Purswosunu et al. 2006 [54]	Postmenopausal, female, osteoporosis	Indonesia	30	33	Ca, 1.5 g MK-4, 45 mg	Ca, 1.5 g Placebo	1 year	60.6 (5.7)	60.9 (4.9)
Ronn et al. 2016 (3-year follow-up to publish) [53]	Healthy, postmenopausal, female, osteopenia	Denmark	71	71	Ca, 800 mg VD, 38 μg MK-7, 375 μg	Ca, 800 mg VD, 38 μg Placebo	1 year	67.0 (4.5)	67.9 (4.6)

Table 1 (continued)

Author, year	Population	Country	Randomised (*n*)		Intervention (type, dose)	Control	Follow-up (months)	Age, (years [SD])	
			Control	Vitamin K				Control	Vitamin K
Sasaki 2005 [55]	Chronic glomerulonephritis patients	Japan	10	10	Glucocorticoids MK-4, 45 mg	Glucocorticoids	1 year	38.5 (6.4)	41.6 (7.2)
Shiomi 2005 [56]	Cirrhosis + viral hepatitis, female	Japan	22	23	MK-4, 45 mg	None	2 years	59 (9)	61 (8)
Shiraki 2000 [58]	Osteoporosis, female	Japan	121	120	Ca, 150 mg MK-4, 45 mg	Ca, 150 mg	2 years	68.0 (0.8)	66.4 (0.8)
Shiraki and Itabashi 2009 [57]	Postmenopausal, female, osteoporosis	Japan	60	62	Ca, 1.2 g MK-4, 45 mg	Ca, 1.2 g	6 months	69.3 (7.4)	67.8 (7.9)
Somekawa 1999 [59]	Female, uterine leiomyomas/ endometriosis	Japan	52	52	Leuprolide acetate, 1.88 mg/month MK-4, 45 mg Leuprolide acetate, 1.88 mg/month MK-4, 45 mg VD, 0.5 μg	Leuprolide acetate, 1.88 mg/month Leuprolide acetate, 1.88 mg/month VD, 0.5 μg	6 months	46 (1)	46 (1)
Tanaka et al. 2017 [60]	Female, osteoporosis, >65 years	Japan	991	992	Risedronate, 2.5 mg MK-4, 45 mg	Risedronate, 2.5 mg	2 years	75.3 (5.9)	75.3 (5.8)
Ushiroyama 2001 [61]	Postmenopausal, female	Japan	65	61	MK-4, 45 mg MK-4, 4 5 mg VD, 1 μg	None VD, 1 μg	2 years	53.2 (5.8)	53.7 (6.1)
Volpe et al. 2008 [62]	Pre and peri menopausal women	America	10	11	K1, 600 μg	Placebo	6 months	37.05 (9.55)	35.36 (8.02)
Yuko 2014 [63]	Chronic glomerulonephritis	Japan	19	23	Risedronate 17.5 mg (week) MK-4, 45 mg	Risedronate 17.5 mg (week)	6 months	39.4 (17.0)	NR

Ca, calcium; *Zn,* zinc; *VD*, vitamin D; *Mag*, magnesium; *K1*, vitamin K1; *MK-4*, menaquinone-4; *MK-7*, menaquinone-7; *NR*, not reported

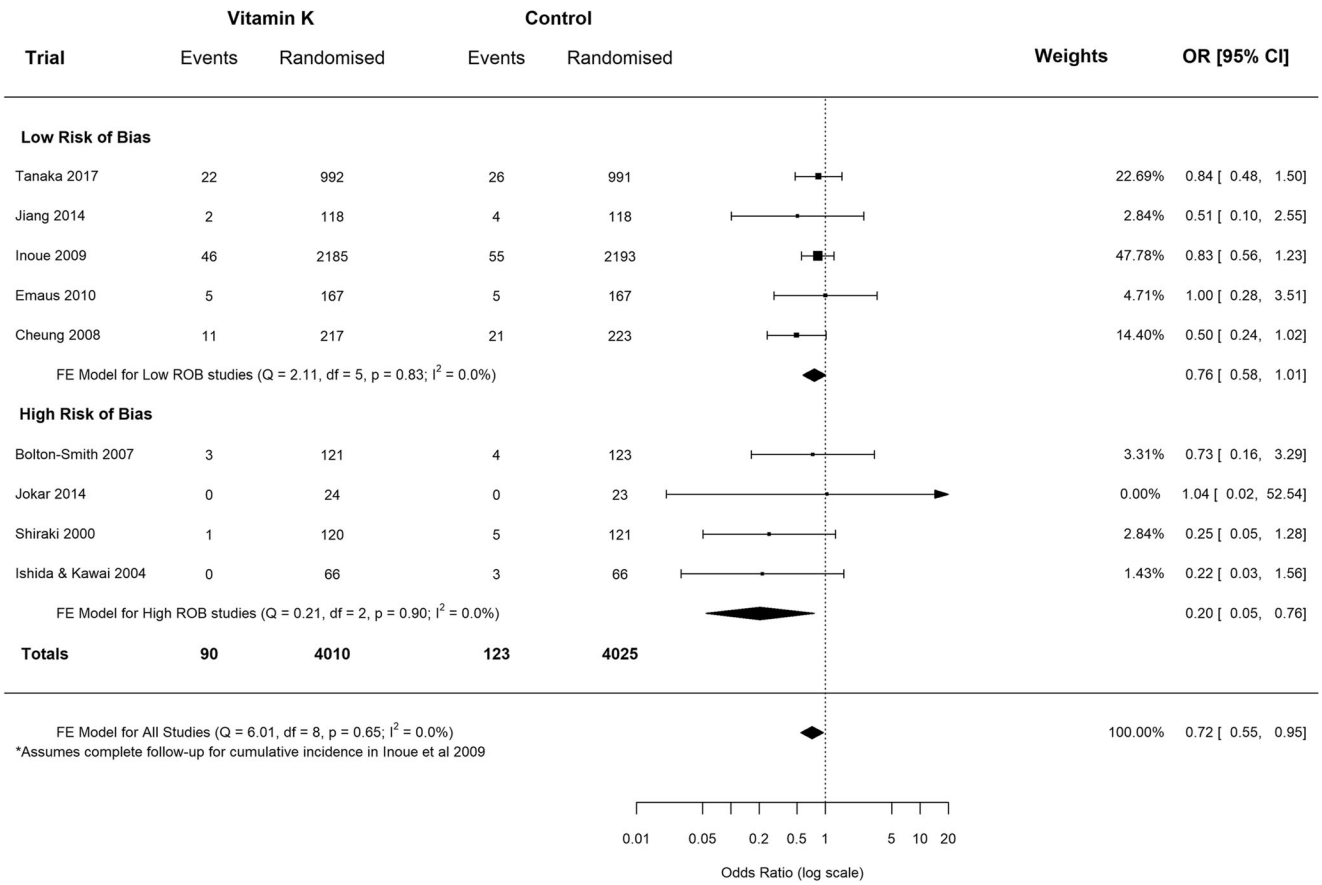


Fig. 2 Meta-analysis of Peto odds ratio of any clinical fracture outcomes for trials including osteoporotic or postmenopausal participants

bias were classified as having a high risk of bias if randomisation procedures were not clearly described.

Statistics

To assess the overall quality of the randomisation in the trials included in the meta-analysis, heterogeneity of age was assessed using the method specified by Hicks et al. [20]. For multi-arm trials, where appropriate, the separate treatment arms were pooled for all analyses; each arm was used only once.

For fracture outcomes, a meta-analysis of odds ratios (ORs) was used. As fracture rates were expected to be low, a fixed-effects meta-analysis using the Peto odds ratio method was used with no correction for zero event counts [21]. For BMD outcomes, a random-effects meta-analysis of weighted mean difference in percentage change from baseline was used at the four anatomical sites at 6 months, 1 year and 2 years.

The heterogeneity of each meta-analysis was assessed using Cochran's Q and the I^2 statistic, using the interpretation thresholds suggested by the Cochrane handbook [21]. For each meta-analysis, a funnel plot was used to assess potential publication bias; for any meta-analysis where 10 or more studies were available, an Egger weighted regression test was undertaken [22].

Sensitivity analyses were undertaken, accounting for the effect of risk of bias in individual studies when a suitable number of studies were available for an outcome.

All analyses were undertaken in R and the metafor package was used for all meta-analyses [23, 24].

Results

Study selection

Our search identified 470 records, and after de-duplication, 275 were available for screening. Of the 275 screened, 47 were included for full-text review along with the 8 records from the original review. Two further records were identified through hand searching of references and the full-texts of these articles were reviewed. Following full-text review, 44 records were eligible for inclusion describing 38 studies [25–63]. A further two ongoing studies that may be eligible, once completed, were identified in our searches [64, 65]. One of the included studies has completed a longer-term follow-up

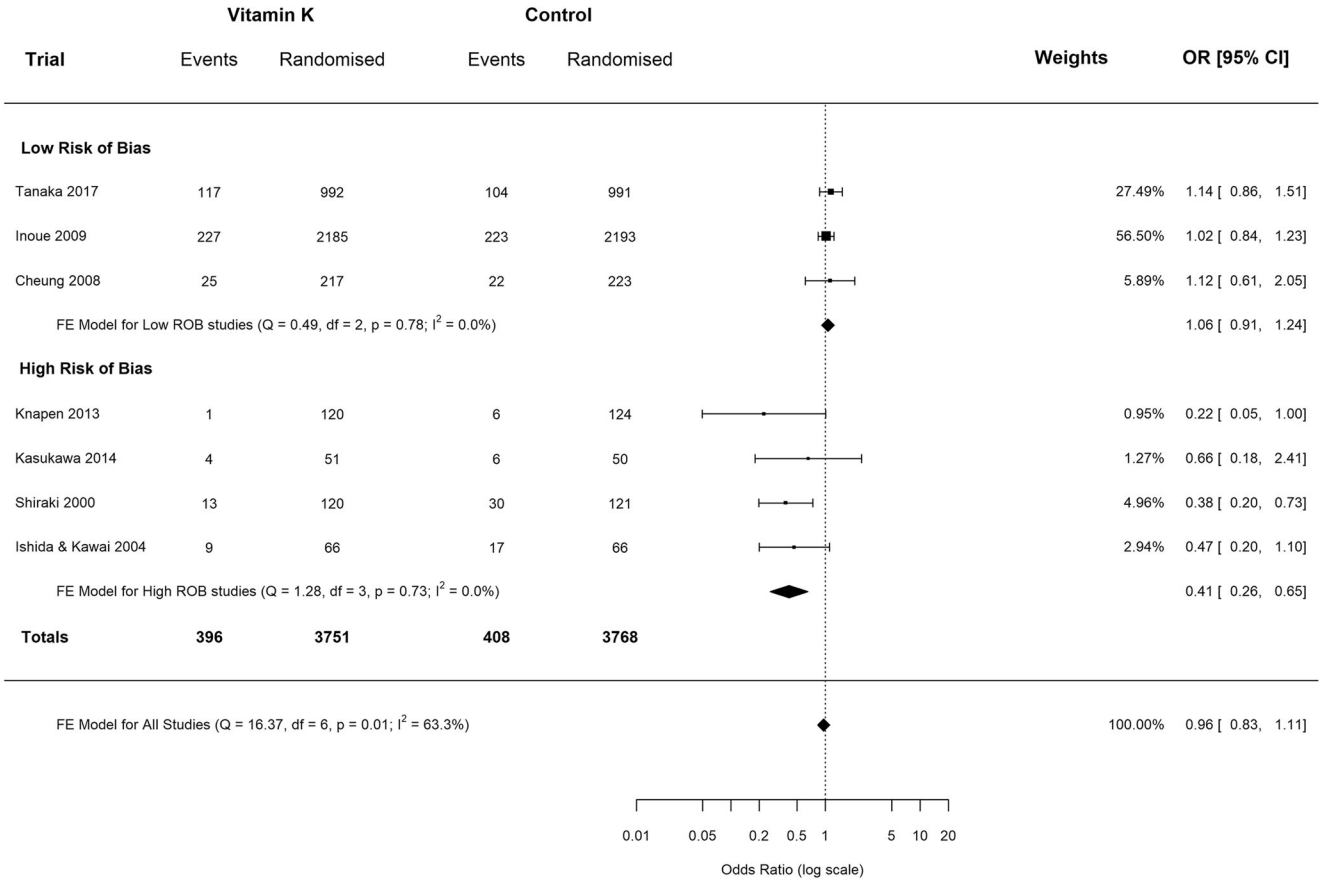


Fig. 3 Meta-analysis of Peto odds ratio of any vertebral fracture outcomes for trials including osteoporotic or postmenopausal participants

but has yet to report [53]. The decision for each full-text record that was screened can be found in Supplement 2.

A flow diagram of the number of records at each stage can be seen in Fig. 1.

Study characteristics

The 36 included studies had a total of 11,112 participants with follow-up ranging from 6 to 48 months. Twenty-four of the trials included postmenopausal women with or without osteoporosis, three included patients with cirrhosis, two included patients with chronic glomerular nephritis, and of the remaining trials, two were in healthy populations and five were in patient populations. Thirteen of the trials were placebo-controlled. Sixteen of the trials were conducted in Japan. Table 1 shows a summary of the study characteristics for the included trials. Details of outcome reporting can be seen in Supplement 3 and 4.

We classified 19 trials as being at high risk of bias and 17 trials as being at low risk of bias. The decisions and classifications for each trial can be seen in Supplement 5.

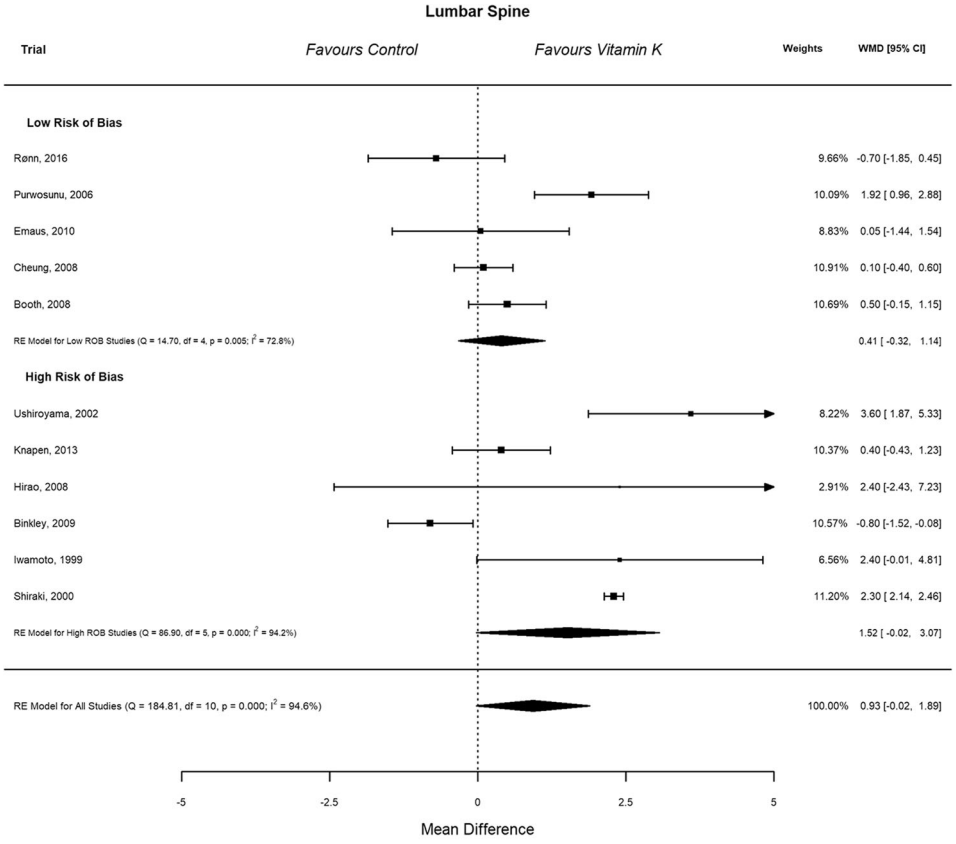
Meta-analyses

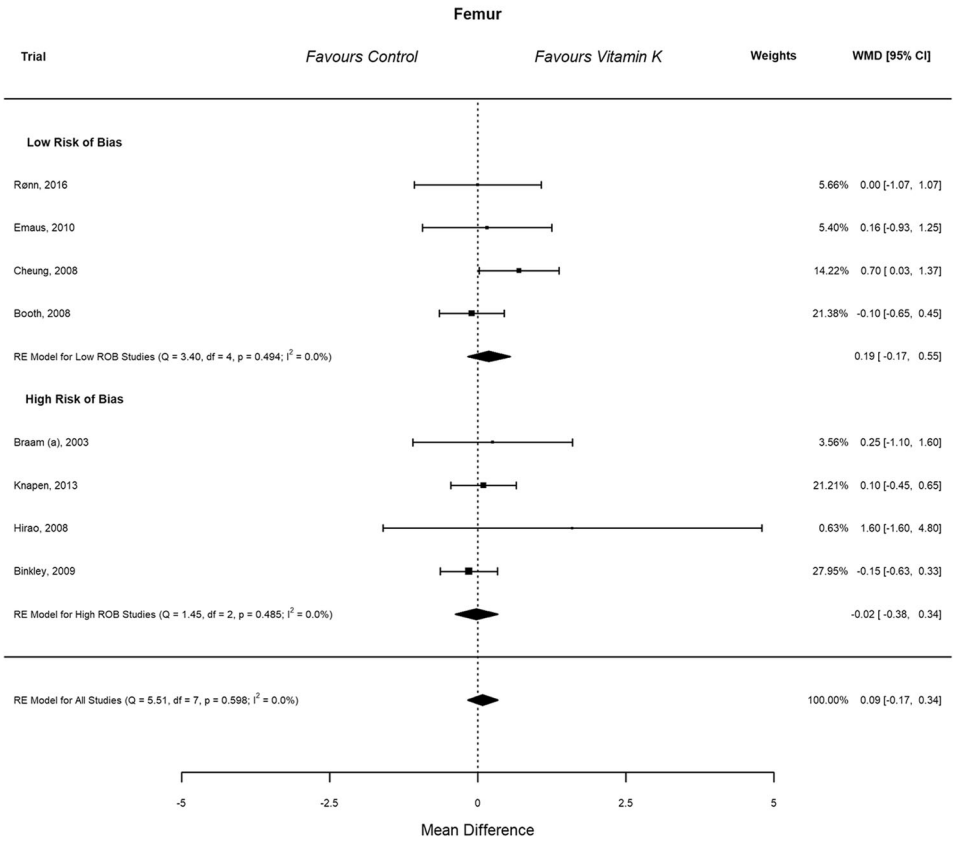
A test for baseline heterogeneity of age revealed no concerning heterogeneity (Supplement 6).

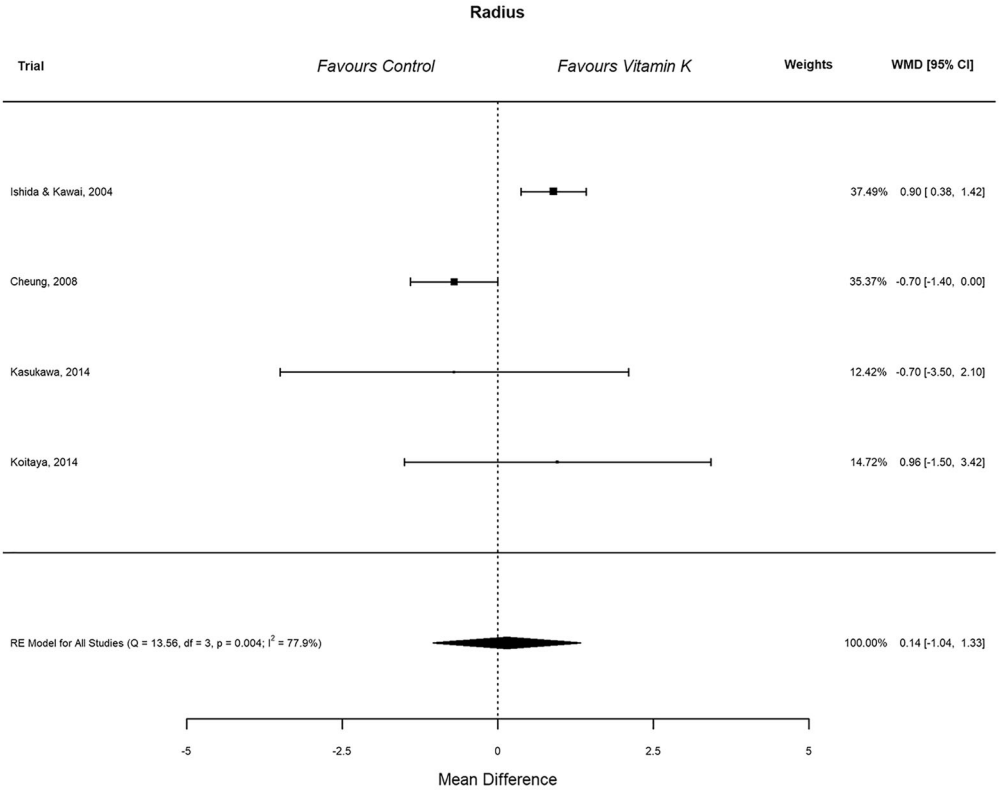
Fractures

Fracture data were available for 12 trials, nine reported total clinical fractures, eight reported vertebral fractures, and hip fractures were reported by only one trial (Supplement 3). Cheung et al. reported hip fractures; there were none reported in the vitamin K group and one reported in the placebo group; this trial was classified as low risk of bias; the trial assessed 5 mg vitamin K1 against placebo with both groups also receiving calcium and vitamin D [30]. Of the trials that reported other clinical fracture outcomes, 11 studies were conducted solely in postmenopausal or osteoporotic women and one was in chronic glomerulonephritis patients (Sasaki et al); these

Fig. 4 Meta-analysis of mean difference in percentage change from baseline in bone mineral density at 12 months for trials including osteoporotic or postmenopausal participants ▶


Lumbar Spine
Trial
Favours Control
Favours Vitamin K
Weights
WMD [95% CI]
Low Risk of Bias
Rønn, 2016 9.66% -0.70 [-1.85, 0.45]
Purwosunu, 2006 10.09% 1.92 [0.96, 2.88]
Emaus, 2010 8.83% 0.05 [-1.44, 1.54]
Cheung, 2008 10.91% 0.10 [-0.40, 0.60]
Booth, 2008 10.69% 0.50 [-0.15, 1.15]
RE Model for Low ROB Studies (Q = 14.70, df = 4, p = 0.005; I² = 72.8%) 0.41 [-0.32, 1.14]
High Risk of Bias
Ushiroyama, 2002 8.22% 3.60 [1.87, 5.33]
Knapen, 2013 10.37% 0.40 [-0.43, 1.23]
Hirao, 2008 2.91% 2.40 [-2.43, 7.23]
Binkley, 2009 10.57% -0.80 [-1.52, -0.08]
Iwamoto, 1999 6.56% 2.40 [-0.01, 4.81]
Shiraki, 2000 11.20% 2.30 [2.14, 2.46]
RE Model for High ROB Studies (Q = 86.90, df = 5, p = 0.000; I² = 94.2%) 1.52 [-0.02, 3.07]
RE Model for All Studies (Q = 184.81, df = 10, p = 0.000; I² = 94.6%) 100.00% 0.93 [-0.02, 1.89]
-5
-2.5
0
2.5
5
Mean Difference


Femur
Trial
Favours Control
Favours Vitamin K
Weights
WMD [95% CI]
Low Risk of Bias
Rønn, 2016 5.66% 0.00 [-1.07, 1.07]
Emaus, 2010 5.40% 0.16 [-0.93, 1.25]
Cheung, 2008 14.22% 0.70 [0.03, 1.37]
Booth, 2008 21.38% -0.10 [-0.65, 0.45]
RE Model for Low ROB Studies (Q = 3.40, df = 4, p = 0.494; I² = 0.0%) 0.19 [-0.17, 0.55]
High Risk of Bias
Braam (a), 2003 3.56% 0.25 [-1.10, 1.60]
Knapen, 2013 21.21% 0.10 [-0.45, 0.65]
Hirao, 2008 0.63% 1.60 [-1.60, 4.80]
Binkley, 2009 27.95% -0.15 [-0.63, 0.33]
RE Model for High ROB Studies (Q = 1.45, df = 2, p = 0.485; I² = 0.0%) -0.02 [-0.38, 0.34]
RE Model for All Studies (Q = 5.51, df = 7, p = 0.598; I² = 0.0%) 100.00% 0.09 [-0.17, 0.34]
-5
-2.5
0
2.5
5
Mean Difference



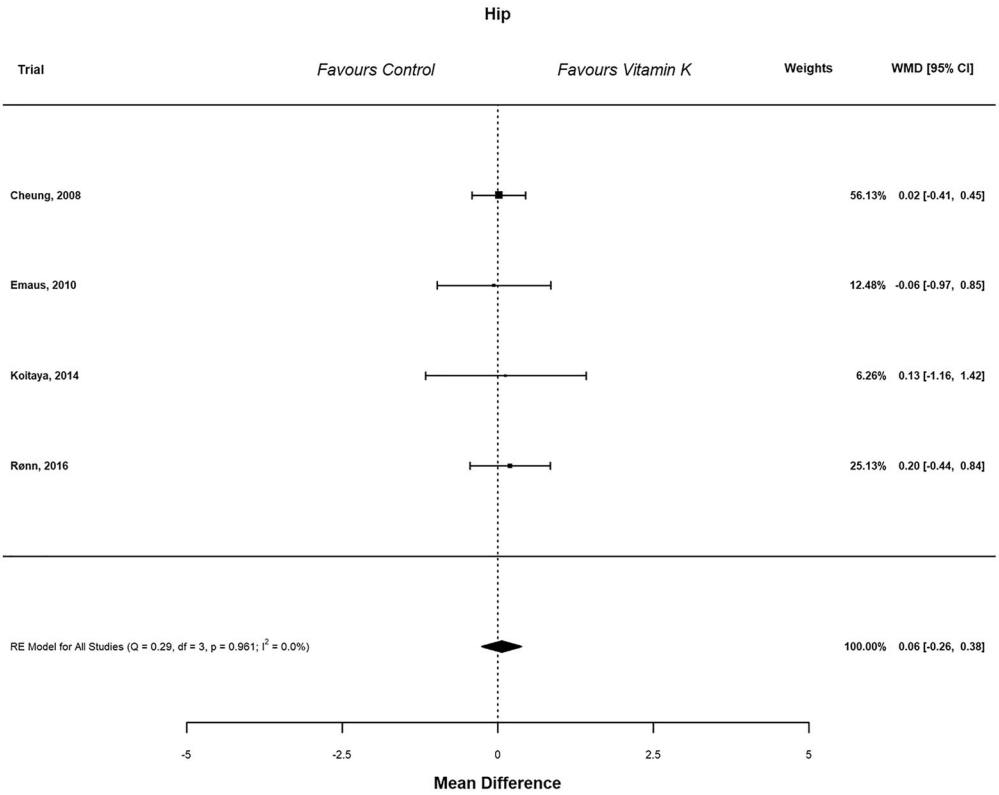


Fig. 4 continued.

two groups were deemed too clinically heterogeneous to be combined in meta-analyses.

Sasaki et al. recruited 20 patients with chronic glomerulonephritis and randomised these patients (1:1) to either glucocorticoids alone or glucocorticoids and 45 mg/day vitamin K (MK-4) [55]. A vertebral fracture was seen in one patient in the glucocorticoids alone group and no patients in the vitamin K and glucocorticoids group. No information is provided on the diagnosis criteria used for vertebral fracture and this study was classified as being at a high risk of bias.

All the trials reporting vertebral fractures used similar criteria for the diagnosis of a vertebral fracture, all looking for a minimum of 20–25% reduction in vertebral height relative to baseline using one of two methods [66, 67]. Methods for the diagnosis of clinical fracture differed between the studies with Cheung, Inoue, Tanaka and Shiraki all confirming fractures using radiography at the time of fracture; Emaus collected self-reported fractures at each follow-up from the participants; all the other trials did not report their method for the diagnosis or reporting of fractures.

Of the trials reporting clinical fractures, six used vitamin K2 (five with 45 mg MK-4, one with 360 μg MK-7) and three used vitamin K1 (ranging from 200 μg to 10 mg). Of the trials reporting vertebral fractures, six used vitamin K2 (five with 45 mg MK-4, one with 360 μg MK-7) and one used vitamin K1 (5 mg).

Meta-analyses were undertaken for both total clinical fractures and vertebral fractures for all trials including osteoporotic or postmenopausal women. For total clinical fractures, a statistically significant odds ratio (OR) of 0.72 (95%CI 0.55 to 0.95) was observed, representing a lower odds of fractures for those taking vitamin K (2.24% vs 3.06%) (Fig. 2). The vertebral fractures meta-analysis showed a non-statistically significant OR of 0.96 (95%CI 0.83 to 1.11) with those taking vitamin K having fewer fractures (10.55% vs 10.82%) (Fig. 3). Sensitivity analysis showed that in low risk of bias trials, there was no statistically significant effect between control and vitamin K seen in either total clinical (2.34% vs 3.01%; OR 0.76, 95%CI 0.58 to 1.02) or vertebral fractures (10.87% vs 10.24%; OR 1.06, 95%CI 0.91 to 1.24). Substantial heterogeneity was observed in the vertebral fractures meta-analysis; however, no heterogeneity was present in the sensitivity analysis.

The funnel plot for total clinical fractures showed no concerning asymmetry (Supplement 7). However, the funnel plot for vertebral fractures showed some asymmetry; this appears to be due to the studies with high and low risk of bias presenting differing results (Supplement 8).

Bone mineral density

Thirty-six trials reported collecting BMD data (Supplement 4). Twenty-two of these trials included postmenopausal or osteoporotic women and provided data that could be combined in meta-analyses for our pre-specified time-points. Both the K1 and K2 forms of vitamin K were used in the included trials with the K1 doses ranging from 100 μg to 5 mg and the K2 doses ranging from 180 μg to 45 mg.

At 6 months, the percentage change in BMD was statistically significantly higher for those receiving vitamin K supplementation at the hip (mean difference [MD] 0.42%, 95% confidence interval [CI] 0.01 to 0.83) and the femur 0.29% (95%CI 0.17 to 0.42) but was not statistically significantly different at the lumbar spine or the radius (Supplement 9). At 1 year, BMD was not statistically significantly different between the vitamin K and control groups (Fig. 4). At 2 years, the change in BMD was statistically significantly higher in the vitamin K group at the lumbar spine (MD 1.63%, 95%CI 0.10 to 3.16) and the femur (MD 0.45, 95%CI 0.05 to 0.85), but no statistically significant change was seen at other sites (Fig. 5). Considerable heterogeneity was observed for the lumbar spine at the 6-month and 1-year time-points and for the radius at 1 and 2 years. Only one trial reported hip BMD at 24 months which indicated no difference between the groups (MD 0.19%, 95%CI − 0.38 to 0.77) [30].

Sensitivity analyses accounting for the individual risk of bias in the studies showed that for studies with a low risk of bias, the percentage change in lumbar spine at 6 months was higher for the controls than vitamin K (MD − 0.21, 95%CI − 0.38 to − 0.03), and that there was no statistically significant difference at 1 year (MD 0.41, 95%CI − 0.32 to 1.14), or 2 years (MD − 0.04, 95%CI − 0.53 to 0.46). The sensitivity analyses also confirmed that there was no statistically significant difference in BMD at the femur at 1 year (MD 0.19, 95%CI − 0.17 to 0.55). Heterogeneity remained high at the lumbar spine at 1 year in the sensitivity analysis, although this appears to be caused by the inclusion of one study [54].

The funnel plots for BMD outcomes did not show any concerning asymmetry; Egger weighted regression for the lumbar spine at 1 year meta-analyses confirmed a lack of significant asymmetry (Supplement 10, 11, 12).

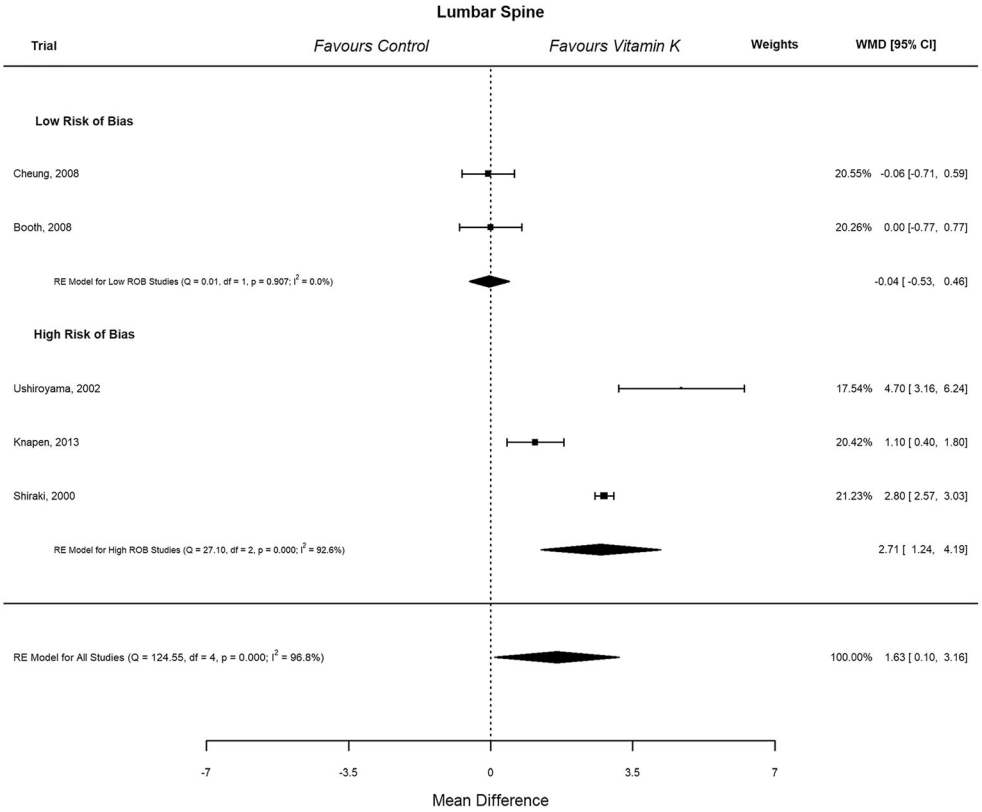
A summary of studies in other patient groups is provided in supplement 13 as these were not suitable for meta-analysis.

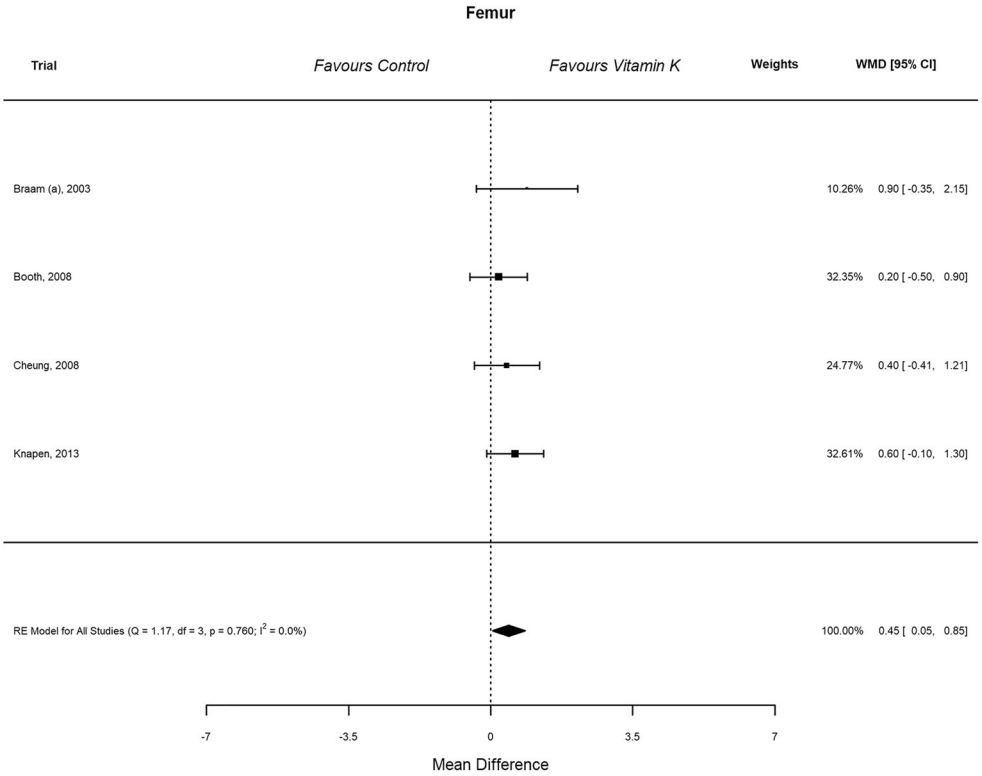
Discussion

Summary of evidence

The majority of trials identified in this systematic review were conducted in postmenopausal or osteoporotic patients. For other groups of patients, there is limited evidence on the effect of vitamin K supplementation on fractures or BMD; therefore, no conclusions can be drawn on its clinical benefit for these groups.

For postmenopausal and osteoporotic patients, clinical fractures were lower in the vitamin K group (2.24% vs


Lumbar Spine
Trial
Favours Control
Favours Vitamin K
Weights
WMD [95% CI]
Low Risk of Bias
Cheung, 2008
20.55% -0.06 [-0.71, 0.59]
Booth, 2008
20.26% 0.00 [-0.77, 0.77]
RE Model for Low ROB Studies (Q = 0.01, df = 1, p = 0.907; I² = 0.0%)
-0.04 [-0.53, 0.46]
High Risk of Bias
Ushiroyama, 2002
17.54% 4.70 [3.16, 6.24]
Knapen, 2013
20.42% 1.10 [0.40, 1.80]
Shiraki, 2000
21.23% 2.80 [2.57, 3.03]
RE Model for High ROB Studies (Q = 27.10, df = 2, p = 0.000; I² = 92.6%)
2.71 [1.24, 4.19]
RE Model for All Studies (Q = 124.55, df = 4, p = 0.000; I² = 96.8%)
100.00% 1.63 [0.10, 3.16]
-7
-3.5
0
3.5
7
Mean Difference


Femur
Trial
Favours Control
Favours Vitamin K
Weights
WMD [95% CI]
Braam (a), 2003
10.26% 0.90 [-0.35, 2.15]
Booth, 2008
32.35% 0.20 [-0.50, 0.90]
Cheung, 2008
24.77% 0.40 [-0.41, 1.21]
Knapen, 2013
32.61% 0.60 [-0.10, 1.30]
RE Model for All Studies (Q = 1.17, df = 3, p = 0.760; I² = 0.0%)
100.00% 0.45 [0.05, 0.85]
-7
-3.5
0
3.5
7
Mean Difference

◀ **Fig. 5** Meta-analysis of mean difference in percentage change from baseline in bone mineral density at 24 months for trials including osteoporotic or postmenopausal participants

3.06%) with an OR of 0.72; when restricted to low risk of bias studies, the effect was smaller (2.34% vs 3.01%) with an OR of 0.76. The trials in this review that were powered to detect a reduction in the risk of fractures defined the minimum clinically important reduction as being between 20% and 35%. We observed a reduction of 28% in all trials and 24% in trials with a low risk of bias. Whilst a fracture reduction of this magnitude would be considered clinically relevant, the translation of this data to clinical practice is hampered by the high variability in study designs, especially concerning treatment regimens (e.g. form of vitamin K, dosage, co-supplementation with drugs, vitamin D, and minerals, length of treatment, etc.)

The odds of vertebral fractures were lower in the vitamin K group compared to the control group (10.55% vs 10.82%; OR 0.96); however, the odds of fracture were higher in the vitamin K group when the analysis was restricted to low risk of bias trials (10.87% vs 10.24%; OR 1.06). This suggests that vitamin K is unlikely to have an effect on vertebral fracture and that if it does, this effect is unlikely to be clinically significant.

There is insufficient data to suggest an effect of vitamin K on hip fractures in postmenopausal or osteoporotic patients.

A previous systematic review assessing the effect of calcium supplementation on BMD defined an increase of 1 to 2% per year as unlikely to result in a clinically meaningful reduction in fracture risk [68]. The change in BMD seen in the full analysis was less than 1% at 1 year and less than 2% at 2 years at all sites, with smaller effects in sensitivity analyses of trials with a low risk of bias. Therefore, if vitamin K does exert an effect on BMD, it is unlikely to yield a beneficial clinical effect.

Another recent systematic review found that the clinical use of oral vitamin K antagonists (VKA) for anticoagulant therapy was not associated with an increased fracture risk, neither did they reduce BMD beyond the effects seen in medical illness [69]. This lack of effect on BMD or fractures was observed irrespective of duration of VKA use [69] and knowledge that exposure to even low doses of VKA raises the fraction of ucOC/OC to extremely high levels [70]. This supports our results that vitamin K is unlikely to have a clinically meaningful effect on BMD.

The results of this review differ from those of the original review [1] and other systematic reviews [14, 71, 72] on the use of vitamin K, which have demonstrated a larger effect on fractures and BMD. This difference is likely a result of the inclusion of more recent large trials reporting fracture outcomes, the removal of potentially fraudulent studies in this systematic review, inclusion of all forms of vitamin K and

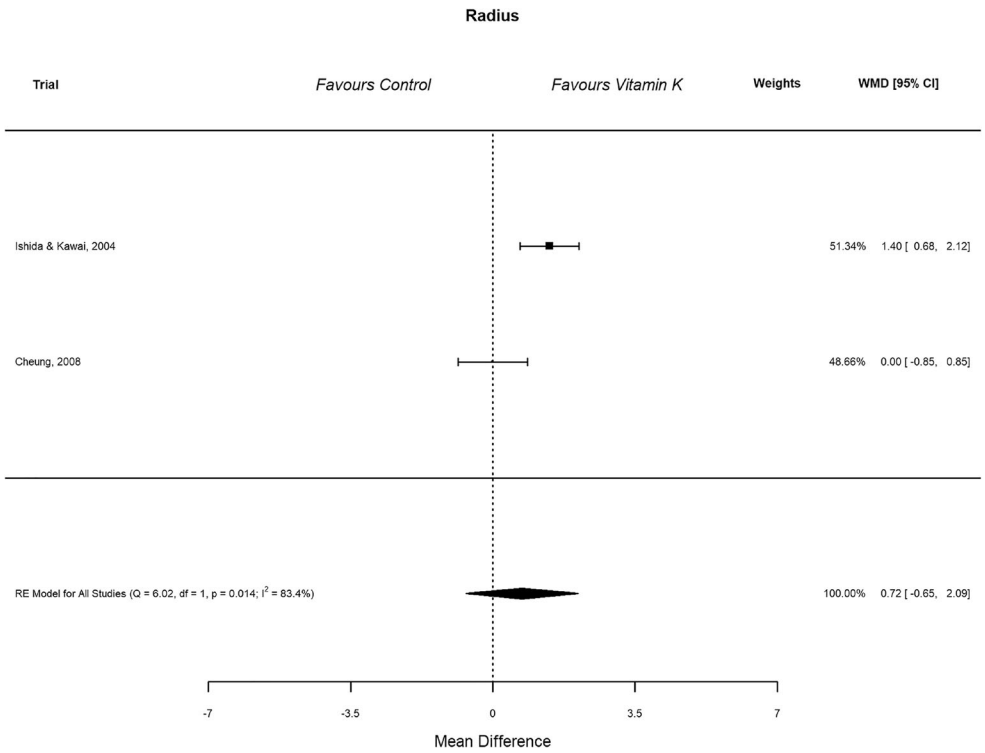


Fig. 5 continued.

accounting for the methodological quality of the included trials in our analyses.

Other biological mechanisms may explain the results seen in this review. For example, there is substantial evidence that the molecule MK-4 is able to modulate cellular functions such as gene expression and signal transduction that control bone processes such as the generation of bone osteoclasts [73]. Note that such a mechanism does not rule out that vitamin K1 acts in the same way because vitamin K1 is a precursor of MK-4 in the human body [73].

Alternatively, there is currently an ongoing trial (ISRCTN18436190) investigating whether vitamin K has an effect on balance, falls and postural blood pressure, which if demonstrated, could explain why the data from this systematic review suggests that vitamin K reduces clinical fractures but not vertebral fractures or bone mineral density.

Strengths and limitations

The main strength of our study was the exclusion of trials that have been reported as questionable and the inclusion of more recent trials that were larger and analysed both BMD and fracture outcomes. The analysis of a larger number of trials with a higher methodological quality allowed planned sensitivity analyses to be undertaken, which allow more robust conclusions regarding the efficacy of vitamin K.

More trials have also been published that are powered to detect an effect on fractures. All the trials used a validated method for the diagnosis of vertebral fractures and only one low risk of bias trial relied on self-reporting of incident clinical fractures. The number of vertebral fractures aligns with those reported in comparable studies. However, the prevalence of vertebral fractures has been reported to be more variable in studies in Asia, which may affect the generalisability of our results [74]. Our analyses still indicate uncertainty regarding the effect of vitamin K supplementation on the rates of total clinical fractures, which may reflect the differing methods for reporting and diagnosis of fractures.

Our study also has limitations. Some trials did not provide suitable data to be combined in meta-analysis. Many of the trials included were conducted in Japanese populations and postmenopausal women; thus, further research is required to draw conclusions for the efficacy of vitamin K in other populations.

Some BMD outcomes had considerable heterogeneity which may be a result of trial methodology, measurement methods, vitamin K form and dosage used, or baseline population characteristics, which could not be explored further. It is also possible that differences in concurrent treatments, such as vitamin D, calcium or bisphosphonates, could influence our results, especially as no trials stratified by baseline vitamin D status in their randomisation protocol. This would allow the trials to mitigate the differing effects of some concurrent treatments on individuals with different baseline values.

Many of the trials provided baseline BMD, which varied between the trials. As there is likely to be little effect in participants with a low fracture risk, the inclusion of participants with normal BMD at baseline may reduce the size of any effect seen on fractures that may be present in those with a low BMD at baseline.

There is also little reporting on baseline vitamin K, as benefit is only likely to be gained in patients who are deficient in vitamin K. However, the question of whether vitamin K supplementation would have had a greater effect in patients with vitamin K deficiency cannot be answered from the available data within these trials for several reasons. Apart from the absence of appropriate baseline data for many trials, there is no common agreement on either the definition of vitamin K deficiency, the assay methodology used to assess it, or how to create and interpret cross assay reference ranges of the various available biomarkers [75]. Standardisation of this should be a priority for any future trials.

The majority of the trials included in our analyses used the MK-4 form of vitamin K2 with a dosage of 45 mg; however, many trials also used vitamin K1 and some MK-7 at various dosages. The fracture meta-analyses showed little statistical heterogeneity between these different forms and doses; however, our results cannot be confirmatory with regard to the relative effectiveness of different vitamin K regimens.

Conclusions

Vitamin K supplementation appears to have little effect on BMD for postmenopausal or osteoporotic patients. Whilst no effect was seen on vertebral fracture outcomes for these patients, a potentially clinically relevant effect was seen on clinical fractures, although further high-quality research is required to confirm this.

Further research might focus on the use of vitamin K supplementation in individuals with a high baseline fracture risk or with clear biochemically defined vitamin K insufficiency, and outcomes that can explore alternative mechanisms of action. The possible value of vitamin K supplementation could also be expanded to other patient groups where evidence is presently lacking.

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Compliance with ethical standards

Conflicts of interest None.

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Data Data and R code are available at https://doi.org/10.6084/m9.figshare.7315040 and https://doi.org/10.6084/m9.figshare.7315064.v1.