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Impact of calcium, vitamin D, vitamin K, oestrogen, isoflavone and exercise on bone mineral density for osteoporosis prevention in postmenopausal women: a network meta-analysis

Zijun Xu[1]†, Huwen Wang[1]†, Yue Shi[1], Qiuming Shen[1], Lhakpa Tsamlag[1], Zezhou Wang[2,3], Shoukai Yu[1], Tian Shen[1], Ying Wang[1] and Yong Cai[1]*

[1]*Department of Community Health and Behavioral Medicine, School of Public Health, Shanghai Jiao Tong University, Shanghai 200000, People's Republic of China*
[2]*Department of Cancer Prevention, Shanghai Cancer Center, Fudan University, Shanghai 200000, People's Republic of China*
[3]*Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200000, People's Republic of China*

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Abstract

The aim of this network meta-analysis is to compare bone mineral density (BMD) changes among different osteoporosis prevention interventions in postmenopausal women. We searched MEDLINE, Embase and Cochrane Library from inception to 24 February 2019. Included studies were randomised controlled trials (RCT) comparing the effects of different treatments on BMD in postmenopausal women. Studies were independently screened by six authors in three pairs. Data were extracted independently by two authors and synthesised using Bayesian random-effects network meta-analysis. The results were summarised as mean difference in BMD and surface under the cumulative ranking (SUCRA) of different interventions. A total of ninety RCT (10 777 participants) were included. Ca, vitamin D, vitamin K, oestrogen, exercise, Ca + vitamin D, vitamin D + vitamin K and vitamin D + oestrogen were associated with significantly beneficial effects relative to no treatment or placebo for lumbar spine (LS). For femoral neck (FN), Ca, exercise and vitamin D + oestrogen were associated with significantly beneficial intervention effects relative to no treatment. Ranking probabilities indicated that oestrogen + vitamin D is the best strategy in LS, with a SUCRA of 97·29 % (mean difference: +0·072 g/cm^2 compared with no treatment, 95 % credible interval (CrI) 0·045, 0·100 g/cm^2), and Ca + exercise is the best strategy in FN, with a SUCRA of 79·71 % (mean difference: +0·029 g/cm^2 compared with placebo, 95 % CrI −0·00093, 0·060 g/cm^2). In conclusion, in postmenopausal women, many interventions are valuable for improving BMD in LS and FN. Different intervention combinations can affect BMD at different sites diversely.

Key words: **Osteoporosis: Prevention: Bone mineral density: Postmenopausal women: Network meta-analysis**

Osteoporosis is a common bone metabolic disease characterised by low bone mass and high fracture risk[1]. Bone mineral density (BMD) decline increases the risk of fragility fractures, mainly of the spinal vertebrae, hip and radius[2]. Hip and radial fractures are usually caused by falling, while vertebral fractures usually occur without external force[3]. Vertebral fractures may result in back pain, decreased body height and deformity[4]. Hip fractures are common at the intracapsular where the femoral neck (FN) is broken. Severe fractures can lead to prolonged bed rest, which increases mortality risk[5]. Hormonal changes in postmenopausal women lead to accelerated bone loss and osteoporosis[6], making them more vulnerable to osteoporosis and fragility fractures.

Ca, vitamin D and exercise are considered to be effective intervention methods to prevent bone loss, as mentioned in worldwide osteoporosis guidelines[6–11]. Guidelines also suggest oestrogens[12], 'natural' oestrogens (isoflavones)[6] and vitamin K[6] supplements for prevention of bone loss in postmenopausal women. Many therapeutic treatments for osteoporosis are provided by guidelines but cannot completely restore bone integrity. People of all ages should pay attention to osteoporosis prevention, especially postmenopausal women[13]. The effects of Ca, vitamin D, vitamin K, oestrogen, isoflavone and exercise singly or in combination on BMD in postmenopausal women have not been investigated in a network so far.

Abbreviations: BMD, bone mineral density; CrI, credible interval; FN, femoral neck; LS, lumbar spine; RCT, randomised controlled trial; SUCRA, surface under the cumulative ranking; YSM, years since menopause.

* **Corresponding author:** Yong Cai, fax +86 21 63850472, email caiyong202028@hotmail.com

† These authors contributed equally to this work and should be considered co-first authors.

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It is uncertain which preventive measures can better reduce bone loss and should be chosen under particular conditions, such as when having limited budget, resource, time or when one is not suitable for a specific intervention.

Network meta-analysis is a relatively new meta-analysis technique that compares the therapeutic effects of different interventions based on both direct and indirect comparisons[14]. A randomised controlled trial (RCT) design can evaluate the effects of an intervention[15]. The aim of the present study is to conduct a network meta-analysis of the existing RCT to compare the BMD changes generated by different combinations of osteoporosis prevention interventions in postmenopausal women and to rank the interventions for practical applications.

Methods

Search strategy and study selection

The present study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement extension for network meta-analysis[16]. We systematically searched MEDLINE, Embase and Cochrane Library from inception of each database to 24 February 2019. The keywords and MeSH terms used in the search strategy included Ca, vitamin D, vitamin K, oestrogen, isoflavone, exercise, postmenopausal, BMD and random. The full search strategies used in MEDLINE, Embase and Cochrane Library are provided in eMethod1 in the Supplement. Searches for Ca, vitamin D, vitamin K, oestrogen, isoflavone and exercise were conducted separately.

To make the present study both rigorous and manageable, six authors followed the same standard to conduct the literature review process in three independent pairs: X. Z. J. and W. H. W., W. Z. Z. and L. T. and S. Q. M. and S. Y. These three pairs of authors independently selected different possible interventions based on titles and abstracts (X. Z. J. and W. H. W.: Ca, vitamin K and exercise; W. Z. Z. and L. T.: vitamin D; S. Q. M. and S. Y.: oestrogen and isoflavone). All relevant systematic reviews and meta-analyses were reviewed to extract extra eligible trials. After removing duplicated trials from the databases and from systematic reviews and meta-analyses, the full texts of potentially relevant trials were reviewed by two authors independently (X. Z. J. and W. H. W.). Any disagreement between the two authors was resolved by consensus after discussion with a third investigator (C. Y.).

Inclusion and exclusion criteria

The inclusion criteria were as follows:

(1) Study design: RCT and quasi-RCT, which uses a quasi-random method (such as medical record number) for allocating participants to different interventions;
(2) Participants: postmenopausal women with natural or surgical menopause;
(3) Intervention: single or combined treatment with Ca, vitamin D, vitamin K, oestrogen, isoflavone and exercise;
(4) Comparison: no treatment, placebo for supplements or any intervention mentioned in (3);
(5) Outcome: absolute mean difference in BMD, measured by dual-energy X-ray absorptiometry[17];
(6) Time: study duration longer than 2 months.

Trials were excluded if:

(1) they were abstracts, letters, conference reports without full text, duplications or not published in English;
(2) the investigated postmenopausal women had any disease affecting bone metabolism, including musculoskeletal disease, renal failure, liver disorders, hyperparathyroidism, hyperthyroidism, diabetes mellitus, arthritis or cancer;
(3) the intervention included dietary restriction, health education or other drugs that may affect bone metabolism, including bisphosphonate, fluoride, tamoxifen, calcitonin, corticosteroids, progestin, androgen or placebos for these drugs.

Data extraction and risk-of-bias assessment

Two authors (X. Z. J. and W. H. W.) extracted data from all eligible publications independently. Information including trial name, first author, year of publication, country, population, number of participants, average age, years since menopause (YSM), BMI, study duration, blinding, interventions and mean difference in BMD was extracted.

Two authors (X. Z. J. and W. H. W.) independently assessed the risk of bias with the Cochrane risk of bias assessment tool described in the Cochrane Handbook[18], including the following seven categories: random-sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. Each category was judged as low risk, unclear risk or high risk. Discrepancies in data extraction and risk-of-bias assessment were resolved through discussion.

Statistical analysis

To compare all interventions simultaneously, a Bayesian network meta-analysis using Markov chain Monte Carlo simulation was conducted[19] to incorporate both indirect and direct comparisons. Treatment effects were estimated by random-effects network meta-analysis[20]. The generalised linear models were conducted with a logit link function with four chains and 20 000 iterated simulations, and the initial 5000 iterations were discarded as burn-in.

Effect sizes were summarised as weighted mean differences and 95 % credible intervals (95 % CrI) presented in forest plots. Trials reporting mean difference in BMD without standard deviation or standard error were included in the analysis, with standard deviation or standard error imputed when feasible[18,21]. The correlation between BMD at baseline and the end of intervention was calculated for all studies with complete outcome reports. The mean correlation was used to estimate the standard deviation or standard error in studies without available standard deviation or standard error values[22]. If two or more groups received the same intervention with different dosages, these groups were combined into a single group.

The relative ranking of osteoporosis prevention interventions and BMD changes was presented as rank probabilities and surface under the cumulative ranking (SUCRA) probabilities. SUCRA, which ranges between 0 and 100 %, was calculated by cumulative ranking probability, which represents the likelihood of being the best intervention[23,24]. In the present study, a higher SUCRA score represented a better intervention and increased BMD.

Between-study heterogeneity was assessed using the I^2 statistic, which ranges from 0 to 100 %. Between-study heterogeneity was also assessed by τ, which is independent of the study size[25]. The assumption of transitivity across treatment comparisons was assessed by comparing the distribution of BMI, the potential effect modifier, across the different pairwise comparisons using box plots[26]. Another important prerequisite for effective results is the consistency of direct and indirect evidence from the same treatment comparison, so the node-splitting model was used to assess potential inconsistency[27,28]. Publication bias was assessed using funnel plots[29]. Sensitivity analyses were performed by repeating the meta-analysis using the minimum and maximum correlation values of mean differences in BMD, adjusting the mean differences in BMD according to intervention duration and excluding studies with single group sample size less than 15.

Network meta-analysis was conducted using R software (version 3.5.1) with the gemtc[30] and rjags packages, JAGS (Plummer M, version 4.3.0) and STATA (version 13)[31].

Results

Study selection

A total of 15 041 studies were identified from the three electronic databases (Fig. 1), among which 346 systematic reviews or meta-analyses were considered to be relevant to the topic and received full-text review. Of all the extracted articles considered eligible, 266 were extracted from systematic reviews or meta-analyses and another 549 were identified after screening the titles and abstracts from the databases; 642 articles received full-text review after removing duplicates. Of these studies, a total of ninety RCT met the inclusion criteria.

Study characteristics

The characteristics of the RCT included are summarised in Tables 1 and 2. There were ninety RCT published between 1992 and 2018 that were included, and they had an average duration of 15·6 months. The present study included 10 777 participants with an average age of 62·7 years (range of average age, 42·7–82·4 years), an average YSM of 11·4 (range of average YSM, 0·9–32·5) and an average BMI of 25·4 kg/m^2 (range of average BMI, 19·7–31·0 kg/m^2). The population of three RCT were institutionalised women, and the remaining were non-institutionalised women.

There were eighteen different intervention combination groups presented in the analysis: no treatment, placebo, Ca, vitamin D, vitamin K, oestrogen, isoflavone, exercise, Ca + vitamin D, Ca + vitamin K, Ca + oestrogen, Ca + exercise, vitamin D + vitamin K, vitamin D + oestrogen, isoflavone + exercise, Ca + vitamin D + vitamin K, Ca + vitamin D + exercise and Ca + vitamin D + isoflavone + exercise. The result of transitivity analysis conducted to assess the distribution of BMI across the different pairwise comparisons is shown in online Supplementary Fig. S1.

Among the ninety included RCT, seventy-four of them (*n* 8973, eighteen interventions) reported lumbar spine (LS) BMD, fifty-five (*n* 6707, sixteen interventions) reported FN BMD and 36, 11, 21, 25, 15 and 21 RCT reported trochanter, intertrochanter, Wald's triangle, total hip, radius and total body BMD, respectively. Only the BMD values for LS and FN were included in the network meta-analysis because studies measuring the BMD of these two sites accounted for more than half the number of studies included and involved relatively complete intervention types (a total of eighteen different interventions were available in the present study).

Risk of bias

The risk of bias in the included RCT is shown in the Supplementary material (online Supplementary Table S1 and online Supplementary Fig. S2). Of the ninety RCT, the risk of bias was low for random-sequence generation in thirty-four RCT (37·8 %), allocation concealment in twenty RCT (22·2 %), blinding of participants and personnel in twenty-three RCT (25·6 %), blinding of outcome assessment in eighteen RCT (20·0 %), incomplete outcome data in thirty-six RCT (40·0 %) and other bias in eighty-eight RCT (97·8 %).

Publication bias

Funnel plots for publication bias in the network meta-analysis suggest no evidence of publication bias, but the fact that some studies were not in the 95 % CrI indicates the presence of heterogeneity (online Supplementary Fig. S3).

Lumbar spine

Network meta-analysis for the mean differences in LS BMD included seventy-four RCT (8973 participants) that used eighteen different types of interventions (Fig. 2(a)). The effects of each intervention are presented in Fig. 3(a). Ca (0·015 g/cm^2, 95 % CrI 0·0024, 0·028 g/cm^2), vitamin D (0·019 g/cm^2, 95 % CrI 0·0078, 0·031 g/cm^2), vitamin K (0·027 g/cm^2, 95 % CrI 0·012, 0·42 g/cm^2), oestrogen (0·050 g/cm^2, 95 % CrI 0·033, 0·067 g/cm^2), exercise (0·018 g/cm^2, 95 % CrI 0·010, 0·025 g/cm^2), Ca + vitamin D (0·024 g/cm^2, 95 % CrI 0·011, 0·038 g/cm^2), vitamin D + vitamin K (0·042 g/cm^2, 95 % CrI 0·025, 0·059 g/cm^2) and vitamin D + oestrogen (0·072 g/cm^2, 95 % CrI 0·045, 0·100 g/cm^2) were associated with significantly beneficial effects relative to no treatment. Ca (0·011 g/cm^2, 95 % CrI 0·00052, 0·022 g/cm^2), vitamin D (0·015 g/cm^2, 95 % CrI 0·0028, 0·027 g/cm^2), oestrogen (0·046 g/cm^2, 95 % CrI 0·031, 0·060 g/cm^2) Ca + vitamin D (0·020 g/cm^2, 95 % CrI 0·0068, 0·033 g/cm^2) were associated with beneficial effects compared with placebo. Vitamin D + vitamin K (0·027 g/cm^2, 95 % CrI 0·0092, 0·044 g/cm^2) was associated with positive

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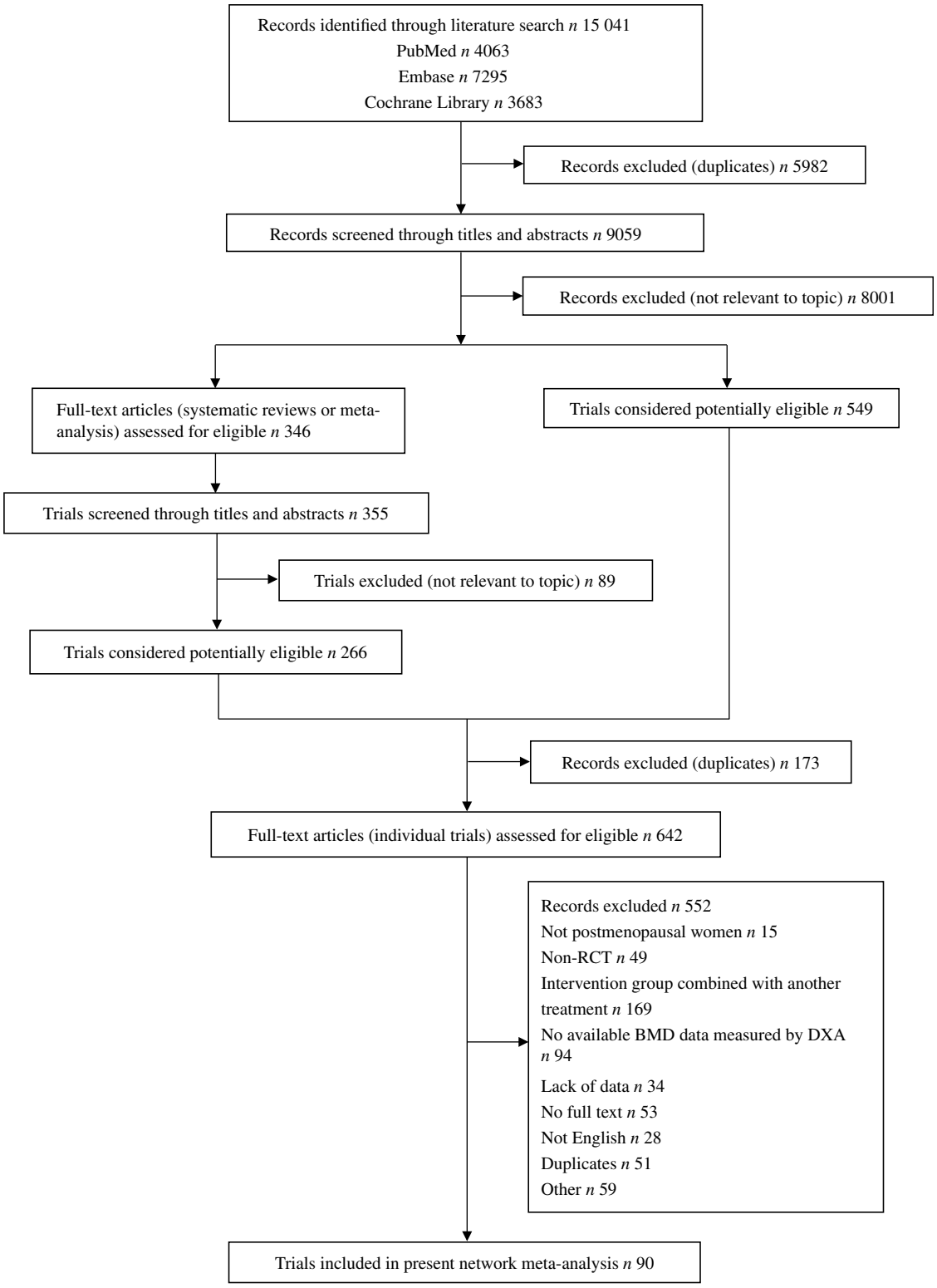

Fig. 1. Flow diagram of literature search and study. RCT, randomised controlled trial; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry.

effect with Ca. Oestrogen (0·031 g/cm^2, 95 % CrI 0·014, 0·047 g/cm^2), vitamin D + vitamin K (0·023 g/cm^2, 95 % CrI 0·0071, 0·039 g/cm^2) and vitamin D + oestrogen (0·053 g/cm^2, 95 % CrI 0·026, 0·080 g/cm^2) were associated with beneficial effect compared with vitamin D. Ca + vitamin D + exercise (0·028 g/cm^2, 95 % CrI 0·0044, 0·053 g/cm^2) had a beneficial effect compared with Ca + vitamin D. Ca + oestrogen (–0·030 g/cm^2, 95 % CrI –0·058, –0·0022 g/cm^2) and isoflavone + exercise (–0·048 g/cm^2, 95 % CrI –0·072, –0·024 g/cm^2) were related to negative effects relative to oestrogen.

Table 1. Description of included trials

	Authors	Publication year	Country	Total *n*	Final *n*	Age	YSM	Duration (months)	Blinding	LS	FN	TC	ITC	WT	TH	TB	Radius
1	Lau *et al.**[32]	1992	China (Hong Kong)	60	50	76·2	NA	10	NA	√	√		√	√			
2	Reid *et al.*[33]	1993	New Zealand	135	122	58·0	9·5	24	Double	√	√	√		√		√	√
3	Hatori *et al.*[34]	1993	Japan	35	33	57·3	7·5	7	NA	√							
4	Nelson *et al.*[35]	1994	USA	40	39	59·2	10·7	12	NA	√	√						
5	Ushiroyama *et al.*[36]	1995	Japan	50	37	51·7	4·3	18	NA	√							
6	Ooms *et al.*[37]	1995	Netherlands	348	244	80·3	32·5	24	Double		√	√					
7	Prince *et al.*[38]	1995	Australia	126	NA	62·7	16·0	24	NA		√	√	√				
8	Pruitt *et al.*[39]	1995	USA	40	26	68·3	NA	12	NA	√	√			√	√		
9	Haines *et al.*[40]	1995	China (Hong Kong)	102	95	42·7	0·9	12	NA	√	√	√		√			
10	Taaffe *et al.*†[41]	1996	USA	36	25	68·1	NA	12	NA								
11	PEPI[42]	1996	USA	349	332	56·1	NA	36	Double	√					√		
12	Lord *et al.*[43]	1996	Australia	179	138	71·6	NA	12	NA	√	√	√					
13	Mizunuma *et al.*[44]	1997	Japan	27	19	55·4	5·9	24	Ppen	√	√	√	√	√			
14	Naessen *et al.*[45]	1997	Sweden	30	25	67·0	NA	6	NA								√
15	Chen *et al.*[46]	1997	Japan	50	45	52·5	3·7	12	Open	√							
16	Dawson-Hughes *et al.*[47]	1997	USA	246	170	71·5	NA	36	Double	√	√					√	
17	Gambacciani *et al.*[48]	1997	Italy	40	25	53·4	4·0	24	NA	√							
18	Riggs *et al.*[49]	1998	USA	236	177	66·3	16·5	48	Double	√						√	
19	Storm *et al.*[50]	1998	USA	40	34	71·5	NA	24	Double	√	√	√					
20	Castelo-Branco *et al.*[51]	1999	Spain	41	35	54·4	NA	24	Open	√							
21	Adami *et al.*[52]	1999	Italy	250	234	64·0	15·0	6	NA	√	√	√		√			√
22	Gorai *et al.*[53]	1999	Japan	79	59	51·6	2·3	24	Open	√	√						
23	Iwamoto *et al.*[54]	1999	Japan	52	52	54·0	5·6	12	NA	√							
24	Ruml *et al.*[55]	1999	USA	63	45	52·8	3·6	24	NA	√	√						√
25	Rhodes *et al.*[56]	2000	Canada	44	38	68·8	NA	12	NA	√	√	√		√			
26	Shiraki *et al.*[57]	2000	Japan	241	180	67·2	18·3	24	Open	√							
27	Iwamoto *et al.*[58]	2000	Japan	92	NA	64·0	15·1	24	NA	√							
28	Ongphiphadhanakul *et al.*[59]	2000	Thailand	96	88	54·5	3·4	24	NA	√	√						
29	Kerr *et al.*[60]	2001	Australia	126	90	60·0	10·7	24	NA	√	√	√	√		√		√
30	Iwamoto *et al.*[61]	2001	Japan	47	NA	65·7	17·1	24	NA								√
31	Chailurkit *et al.*[62]	2001	Thailand	147	NA	NA	NA	24	NA	√	√						
32	Iwamoto *et al.*[63]	2001	Japan	35	NA	64·9	15·1	24	NA	√							
33	Son & Chun[64]	2001	Korea	69	63	72·4	NA	10	NA	√	√	√		√			
34	Arrenbrecht & Boermans[65]	2002	Switzerland	161	121	53·5	10·8	24	Double	√					√		
35	Hans *et al.*[66]	2002	Switzerland	157	102	67·1	NA	24	NA		√	√	√	√	√		
36	Ushiroyama *et al.*[67]	2002	Japan	172	126	53·4	2·9	24	NA	√							
37	Haines *et al.*[68]	2003	China (Hong Kong)	152	139	48·4	NA	12	Double	√					√		
38	Going *et al.*[69]	2003	USA	161	130	56·4	NA	12	NA	√	√	√				√	
39	Jessup *et al.*[70]	2003	USA	20	18	69·2	22·9	8	NA	√							
40	Cooper *et al.*[71]	2003	Australia	187	153	56·3	5·7	24	Double	√	√	√					√
41	Grados *et al.*[72]	2003	France	192	131	74·6	NA	12	Double	√	√	√				√	
42	Uesugi *et al.*[73]	2003	Japan	22	21	53·7	6·0	3	NA	√							
43	Verschueren *et al.*[74]	2004	Belgium	70	NA	64·2	15·7	6	NA	√						√	
44	Chan *et al.*[75]	2004	China (Hong Kong)	132	103	54·0	4·7	12	NA	√	√	√					
45	Ishida & Kawai[76]	2004	Japan	198	186	69·0	19·3	24	NA								√
46	Harwood *et al.*[77]	2004	UK	150	97	81·2	NA	12	Open	√	√	√			√		
47	Inanir *et al.*[78]	2004	Turkey	70	NA	58·4	12·0	6	NA	√	√	√	√	√		√	
48	Englund *et al.*[79]	2005	Sweden	48	40	73·0	23·8	12	Open	√	√	√		√		√	√
49	Moschonis & Manios[80]	2006	Greece	70	62	61·8	10·8	12	NA	√						√	√
50	Yasui *et al.*[81]	2006	Japan	34	30	53·9	6·5	24	NA	√							

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Table 1. (*Continued*)

	Authors	Publication year	Country	Total *n*	Final *n*	Age	YSM	Duration (months)	Blinding	LS	FN	TC	ITC	WT	TH	TB	Radius
51	Korpelainen *et al.*[82]	2006	Finland	160	133	72·9	NA	30	NA		√	√					√
52	Huang *et al.*[83]	2006	China (Taiwan)	43	42	52·4	4·4	12	Open	√	√	√		√			
53	Wu *et al.*[84]	2006	Japan	102	97	54·4	3·2	6	NA	√	√	√			√	√	
54	Nuti *et al.*[85]	2006	Italy	136	102	64·8	16·5	18	Double	√							
55	Maddalozzo *et al.*[86]	2007	USA	NA	58	52·4	2·0	12	NA	√	√	√			√		
56	Woo *et al.*[87]	2007	China (Hong Kong)	90	88	69·5	NA	12	Single	√					√		
57	Bolton-Smith *et al.*[88]	2007	UK	244	209	68·2	19·3	24	Double		√	√		√			√
58	Bergström *et al.*[89]	2008	Sweden	112	92	59·2	NA	12	Open	√					√		
59	Park *et al.*[90]	2008	Korea	50	45	68·4	18·5	11	NA	√	√	√		√			
60	Bocalini *et al.*[91]	2009	Brazil	35	25	68·0	NA	12	NA	√	√						
61	Beck & Norling[92]	2010	Australia	47	42	71·5	NA	8	NA	√	√	√				√	√
62	Tolomio *et al.*[93]	2010	Italy	160	125	63·1	13·1	11	Single		√						
63	Yoo *et al.*[94]	2010	Korea	28	21	71·0	16·6	3	NA	√	√	√		√		√	
64	Chailurkit *et al.*[95]	2010	Thailand	397	336	65·8	NA	24	Double	√	√				√		
65	Kärkkäinen *et al.*[96]	2010	Finland	603	593	67·4	18·1	36	Open	√	√	√		√		√	
66	Verschueren *et al.**[97]	2011	Belgium	113	103	79·6	NA	6	NA						√		
67	Choquette *et al.*[98]	2011	Canada	75	61	59·1	9·1	6	Double	√	√	√		√	√	√	
68	Marques *et al.*[99]	2011	Portugal	60	49	69·9	13·0	8	NA	√	√	√	√				
69	Marques *et al.*[100]	2011	Portugal	71	54	69·0	13·3	8	NA		√	√	√		√		
70	Tartibian *et al.*[101]	2011	Iran	38	NA	60·2	NA	6	NA	√	√						
71	Je *et al.*[102]	2011	Korea	78	45	67·8	17·6	6	NA	√	√						
72	Karakiriou *et al.*[103]	2012	Greece	32	NA	53·3	4·6	6	NA	√							
73	Macdonald *et al.*[104]	2013	UK	305	264	64·6	NA	12	Double	√					√		
74	Basat *et al.*[105]	2013	Turkey	42	35	55·9	13·1	6	NA	√	√						
75	Chilibeck *et al.*[106]	2013	Canada	173	149	56·0	NA	24	Double	√	√	√	√	√	√	√	
76	Rajatanavin *et al.*[107]	2013	Thailand	404	343	65·8	16·4	24	Double	√	√						
77	Lai *et al.*[108]	2013	China (Taiwan)	32	28	60·1	10·2	6	Open	√							
78	Leung *et al.*[109]	2014	China (Hong Kong)	710	596	73·0	23·0	18	Single	√					√		
79	Jiang *et al.*[110]	2014	China	236	213	64·4	15·3	12	Double	√		√					
80	Koitaya *et al.*[111]	2014	Japan	48	48	58·4	7·3	12	Double						√	√	√
81	Moreira *et al.*[112]	2014	Brazil	108	100	58·8	NA	6	NA	√	√					√	
82	Nicholson *et al.*[113]	2015	Australia	57	50	65·8	NA	6	NA	√	√	√			√	√	
83	Santin-Medeiros *et al.*[114]	2015	Spain	43	37	82·4	NA	8	NA		√	√	√	√	√		
84	Tankisheva *et al.*[115]	2015	Belgium	35	31	76·7	NA	6	NA						√		
85	Wang *et al.*[116]	2015	China	119	106	58·5	NA	12	NA	√	√			√			
86	Wen *et al.*[117]	2017	China (Taiwan)	48	46	58·2	6·0	2·5	NA						√	√	
87	Shin *et al.**[118]	2018	Korea	41	37	55·9	7·9	3	Single	√	√						
88	de Oliveira *et al.*[119]	2018	Brazil	51	51	55·4	8·8	6	Single	√	√	√	√	√	√		
89	Aboarrage Junior *et al.*[120]	2018	Brazil	25	25	65·0	NA	6	NA	√	√					√	
90	Bislev *et al.*[121]	2018	Denmark	81	81	NA	NA	3	Double	√	√				√	√	√

YSM, years since menopause; LS, lumbar spine; FN, femoral neck; TC, trochanter; ITC, intertrochanter; WT, Ward's triangle; TH, total hip; TB, total body; NA, not available; PEPI, Postmenopausal Estrogen/Progestin Interventions.
* Institutionalised women.
† Only have thigh bone mineral density.

Table 2. Description of individual groups in included trials*

	Authors	Publication year	Baseline *n*	Loss *n*	Final *n*	Age (years)	YSM	BMI (kg/m^2)	Intervention
1	Lau *et al.*[32]	1992	NA	NA	15	76·0	NA	NA	Ca (800 mg/d) + Ex (load-bearing, 4 d/week)
			NA	NA	11	79·0	NA	NA	Ex (load-bearing, 4 d/week)
			NA	NA	12	75·0	NA	NA	Ca (800 mg/d)
			NA	NA	12	75·0	NA	NA	Placebo
2	Reid *et al.*[33]	1993	NA	NA	61	58·0	9·0	NA	Ca (1000 mg/d)
			NA	NA	61	58·0	10·0	NA	Placebo
3	Hatori *et al.*[34]	1993	23	2	12	56·0	7·5	23·3	Ex (high intensity, 30 min/d, 3 d/week)
					9	58·0	5·8	23·5	Ex (moderate intensity, 30 min/d, 3 d/week)
			12	0	12	58·0	8·9	24·6	No treatment
4	Nelson *et al.*[35]	1994	21	1	20	61·1	11·6	24·4	Ex (strength, 50 min/d, 2 d/week)
			19	0	19	57·3	9·8	23·1	No treatment
5	Ushiroyama *et al.*[36]	1995	15	1	14	53·3	3·7	24·1	D (α-calcidol, 1 μg/d)
			35	12	23	51·0	4·7	24·4	No treatment
6	Ooms *et al.*[37]	1995	177	51	126	80·1	32·6	28·1	D_3 (10 μg/d)
			171	53	118	80·6	32·3	28·6	Placebo
7	Prince *et al.*[38]	1995	42	NA	NA	63·0	16·0	NA	Ca (1000 mg/d) + Ex (4 h/week)
			42	NA	NA	62·0	16·0	NA	Ca (1000 mg/d)
			42	NA	NA	63·0	16·0	NA	Placebo
8	Pruitt *et al.*[39]	1995	15	7	8	67·0	NA	24·5	Ex (high-intensity resistance, 3 d/week)
			13	6	7	67·6	NA	23·9	Ex (low-intensity resistance, 2 d/week)
			12	1	11	69·6	NA	25·1	No treatment
9	Haines *et al.*[40]	1995	49	7	42	42·2	0·6	NA	Est (0·625 mg/d) + Ca (1000 mg/d)
			53	0	53	43·1	1·1	NA	Est (0·625 mg/d)
10	Taaffe *et al.*[41]	1996	12	5	7	67·0	NA	24·5	Ex (high intensity, 3 d/week)
			13	6	7	67·6	NA	23·9	Ex (low intensity, 3 d/week)
			11	0	11	69·6	NA	25·1	No treatment
11	PEPI[42]	1996	175	6	169	56·2	NA	NA	Est (0·625 mg/d)
			174	11	163	55·9	NA	NA	Placebo
12	Lord *et al.*[43]	1996	90	22	68	71·7	NA	NA	Ex (60 min/d, 2 d/week)
			89	19	70	71·5	NA	NA	No treatment
13	Mizunuma *et al.*[44]	1997	14	4	10	55·1	5·2	NA	Est (0·625 mg/d)
			13	4	9	55·8	6·6	NA	No treatment
14	Naessen *et al.*[45]	1997	20	5	15	66·8	NA	NA	Est (17 β-oestradiol, 7·5 μg/d)
			10	0	10	67·5	NA	NA	No treatment
15	Chen *et al.*[46]	1997	25	2	23	52·8	4·4	NA	Ca (150 mg/d) + D_3 (0·75 μg/d)
			25	3	22	52·2	3·0	NA	Ca (150 mg/d)
16	Dawson-Hughes *et al.*[47]	1997	101	24	77	71·0	NA	NA	Ca (500 mg/d) + D (cholecalciferol 17·5 μg/d)
			112	19	93	72·0	NA	NA	Placebo
17	Gambacciani *et al.*[48]	1997	20	7	13	52·9	3·8	24·4	Est (0·3 mg/d) + Ca (500 mg/d)
			20	8	12	53·9	4·1	23·9	Ca (500 mg/d)
18	Riggs *et al.*[49]	1998	119	31	88	66·2	16·5	NA	Ca (1600 mg/d)
			117	28	89	66·3	16·4	NA	Placebo
19	Storm *et al.*[50]	1998	20	3	17	72·0	NA	28·6	Ca (calcium lactate 1000 mg/d)
			20	3	17	71·0	NA	27·8	Placebo
20	Castelo-Branco *et al.*[51]	1999	21	2	19	53·0	NA	22·1	Ca (2·5 mg/d)
			20	4	16	56·0	NA	24·6	No treatment
21	Adami *et al.*[52]	1999	125	7	118	65·0	16·0	24·6	Ex (100 min/d, 2 d/week)
			125	9	116	63·0	14·0	23·8	No treatment
22	Gorai *et al.*[53]	1999	19	2	17	51·5	2·6	21·6	Est (625 mg/d) + D_3 (1 μg/d)
			20	6	14	51·1	2·7	22·4	D_3 (1 μg/d)
			16	3	13	52·3	2·3	21·7	Est (625 mg/d)
			24	9	15	51·5	1·7	23·2	No treatment
23	Iwamoto *et al.*[54]	1999	16	NA	NA	52·6	6·0	23·2	D_3 (1 g/d)
			17	NA	NA	55·9	6·2	22·0	K_2 (45 mg/d)
			19	NA	NA	53·6	4·7	22·5	No treatment
24	Ruml *et al.*[55]	1999	29	12	17	52·1	3·3	NA	Ca (800 mg/d)
			34	6	28	51·7	3·8	NA	Placebo
25	Rhodes *et al.*[56]	2000	22	2	20	68·8	NA	NA	Ex (resistance, 60 min/d, 3 d/week)
			22	4	18	68·2	NA	NA	No treatment
26	Shiraki *et al.*[57]	2000	120	34	86	66·4	17·5	NA	K_2 (45 mg/d) + Ca (150 mg/d)
			121	27	94	68·0	19·1	NA	Ca (150 mg/d)
27	Iwamoto *et al.*[58]	2000	21	NA	NA	63·6	15·0	22·1	D_3 (0·75 μg/d) + K_2 (45 mg/d)
			22	NA	NA	65·8	16·0	21·5	K_2 (45 mg/d)
			29	NA	NA	63·4	14·8	20·8	D_3 (0·75 μg/d)
			20	NA	NA	63·5	14·7	21·0	Ca (calcium lactate 2 g/d)
28	Ongphiphadhanakul *et al.*[59]	2000	34	1	33	53·9	3·2	24·6	D (calcitriol 0·25 μg/d) + Ca (750 mg/d)
			32	2	30	55·0	3·6	25·2	D (calcitriol 0·5 μg/d) + Ca (750 mg/d)
			30	5	25	54·7	3·5	25·0	Ca (750 mg/d)

Table 2. (*Continued*)

	Authors	Publication year	Baseline *n*	Loss *n*	Final *n*	Age (years)	YSM	BMI (kg/m^2)	Intervention
29	Kerr *et al.*[60]	2001	42	18	24	60·0	11·0	NA	Ex (strength, 60 min/d, 3 d/week) + Ca (600 mg/d)
			42	12	30	59·0	9·0	NA	Ex (fitness, 60 min/d, 3 d/week) + Ca (600 mg/d)
			42	6	36	62·0	12·0	NA	Ca (600 mg/d)
30	Iwamoto *et al.*[61]	2001	23	NA	NA	65·4	18·3	20·6	K_2 (45 mg/d)
			24	NA	NA	66·0	16·0	20·9	No treatment
31	Chailurkit *et al.*[62]	2001	32	NA	NA	NA	NA	NA	Ca (750 mg/d) + D (calcitriol 0·5 μg/d)
			33	NA	NA	NA	NA	NA	Ca (750 mg/d) + D (calcitriol 0·25 μg/d)
			36	NA	NA	NA	NA	NA	Ca (750 mg/d)
			46	NA	NA	NA	NA	NA	No treatment
32	Iwamoto *et al.*[63]	2001	8	NA	NA	65·3	16·3	19·7	Ex (2 years) + Ca (calcium lactate 2 g/d) + D_3 (1 μg/d)
			7	NA	NA	64·3	14·7	20·5	Ex (1 year) + Ca (calcium lactate 2 g/d) + D_3 (1 μg/d)
			20	NA	NA	64·9	14·8	19·9	Ca (calcium lactate 2 g/d) + D_3 (1 μg/d)
33	Son & Chun[64]	2001	NA	NA	20	71·8	NA	NA	D (α-calcidol 0·5 μg/d)
			NA	NA	22	72·5	NA	NA	Ca (1000 mg/d)
			NA	NA	21	72·2	NA	NA	Placebo
34	Arrenbrecht & Boermans[65]	2002	54	14	40	53·7	11·1	26·5	E† (oestradiol, 100 μg/d)
			54	11	43	53·7	10·8	26·1	E† (oestradiol, 50 μg/d)
			53	15	38	53·0	10·5	26·6	Placebo
35	Hans *et al.*[66]	2002	99	35	64	67·6	NA	NA	Ex (active)
			32	16	16	66·3	NA	NA	Ex (sham)
			26	4	22	66·0	NA	NA	No treatment
36	Ushiroyama *et al.*[67]	2002	43	12	31	53·3	2·4	21·7	K_2 (45 mg/d) + D_3 (1 μg/d)
			43	11	32	52·8	3·0	22·7	D_3 (1 μg/d)
			43	13	30	54·1	2·6	22·2	K_2 (45 mg/d)
			43	10	33	53·5	3·6	22·9	No treatment
37	Haines *et al.*[68]	2003	50	5	45	46·8	NA	24·2	Est (2 mg/d)
			52	3	49	48·2	NA	23·8	Est (1 mg/d)
			50	5	45	49·2	NA	24·1	Placebo
38	Going *et al.*[69]	2003	91	20	71	55·8	NA	25·8	Ex (3 d/week) + Ca (800 mg/d)
			70	11	59	57·1	NA	25·5	Ca (800 mg/d)
39	Jessup *et al.*[70]	2003	10	1	9	69·4	22·1	NA	Ex (60 min/d, 3 d/week) + Ca (1000 mg/d) + D (10 μg/d)
			10	1	9	69·1	23·7	NA	Ca (1000 mg/d) + D (10 μg/d)
40	Cooper *et al.*[71]	2003	93	20	73	56·5	6·1	NA	Ca (1000 mg/d) + D_2 (250 μg/week)
			94	14	80	56·1	5·4	NA	Ca (1000 mg/d)
41	Grados *et al.*[72]	2003	95	23	72	74·2	NA	27·0	Ca (500 mg/d) + D (10 μg/d)
			97	20	67	75·0	NA	26·4	Placebo
42	Uesugi *et al.*[73]	2003	11	0	11	54·9	6·3	22·3	Iso (61·8 mg/d)
			11	1	10	52·5	5·7	22·8	Placebo
43	Verschueren *et al.*[74]	2004	25	NA	NA	64·6	16·9	26·3	Ex (WBV, 3 d/week)
			22	NA	NA	63·9	15·5	27·4	Ex (resistance, 3 d/week)
			23	NA	NA	64·2	14·6	26·5	No treatment
44	Chan *et al.*[75]	2004	67	13	54	54·4	4·9	24·1	Ex (Tai Chi, 50 min/d, 5 d/week)
			65	16	49	53·6	4·5	23·5	No treatment
45	Ishida & Kawai [76]	2004	66	3	63	68·0	19·0	NA	K_2 (45 mg/d)
			66	3	63	71·0	21·0	NA	D (α-calcidol 1 μg/d)
			66	6	60	68·0	18·0	NA	No treatment
46	Harwood *et al.*[77]	2004	39	13	26	83·0	NA	NA	D_3 (20 μg/d) + Ca (1 g/d)
			36	15	21	81·0	NA	NA	†D_2 (ergocalciferol 7500 μg) + Ca (1 g/d)
			38	10	28	80·0	NA	NA	†D_2 (ergocalciferol 7500 μg)
			37	15	22	81·0	NA	NA	No treatment
47	Inanir *et al.*[78]	2004	40	NA	NA	58·0	12·0	NA	D (calcitriol 0·5 μg/d) + Ca (1000 mg/d)
			30	NA	NA	59·0	12·0	NA	Ca (1000 mg/d)
48	Englund *et al.*[79]	2005	24	3	21	72·8	24·7	25·2	Ex (weight-bearing, 50 min/d, 2 d/week)
			24	5	19	73·2	22·8	26·1	No treatment
49	Moschonis & Manios[80]	2006	30	4	26	62·4	11·4	30·4	Ca (600 mg/d)
			40	4	36	61·4	10·4	30·5	No treatment
50	Yasui *et al.*[81]	2006	17	3	14	54·9	7·5	22·1	K_2 (45 mg/d) + D_3 (0·75 μg/d)
			17	1	16	52·9	5·5	22·5	K_2 (45 mg/d)
51	Korpelainen *et al.*[82]	2006	84	16	68	72·9	NA	25·7	Ex (45 min/d)
			76	11	65	72·8	NA	25·5	No treatment

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Table 2. (*Continued*)

	Authors	Publication year	Baseline *n*	Loss *n*	Final *n*	Age (years)	YSM	BMI (kg/m^2)	Intervention
52	Huang *et al.*[83]	2006	NA	NA	15	51·9	3·1	23·8	Iso (200 mg/d)
			NA	NA	15	53·9	5·6	22·9	Iso (100 mg/d)
			NA	NA	12	51·2	4·4	23·9	No treatment
53	Wu *et al.*[84]	2006	34	3	31	54·4	2·9	22·1	Iso (75 mg/d) + Ex (walking, 60 min/d, 3 d/week)
			34	1	33	53·8	2·7	21·3	Iso (75 mg/d)
			34	1	33	54·9	3·7	20·9	Placebo
54	Nuti *et al.*[85]	2006	69	17	52	65·4	16·2	23·9	D (α-calcidol 1 μg/d)
			67	17	50	64·3	16·8	23·5	Ca (1 g/d) + D_3 (22 μg/d)
55	Maddalozzo *et al.*[86]	2007	35	6	29	52·3	2·1	NA	Ex (50 min/d, 2 d/week)
			34	5	29	52·5	2·0	NA	No treatment
56	Woo *et al.*[87]	2007	30	2	28	69·7	NA	24·4	Ex (Tai Chi, 3 d/week)
			30	0	30	69·6	NA	24·6	Ex (resistance, 3 d/week)
			30	0	30	69·3	NA	24·9	No treatment
57	Bolton-Smith *et al.*[88]	2007	61	12	49	67·8	18·3	26·1	K_1 (200 μg/d) + Ca (1000 mg/d) + D_3 (10 μg/d)
			62	12	50	69·4	21·1	25·8	Ca (1000 mg/d) + D_3 (10 μg/d)
			60	6	54	67·7	17·9	26·4	K_1 (200 μg/d)
			61	5	56	67·8	20·0	26·2	Placebo
58	Bergström *et al.*[89]	2008	60	12	48	58·9	NA	24·4	Ex (fast walk, 30 min/week + training, 60 min/d, 1–2 d/week)
			52	8	44	59·6	NA	24·9	No treatment
59	Park *et al.*[90]	2008	25	3	22	68·3	18·3	NA	Ex (multi-component, 60 min/d, 3 d/week)
			25	2	23	68·4	18·7	NA	No treatment
60	Bocalini *et al.*[91]	2009	23	8	15	69·0	NA	28·0	Ex (resistive, 60 min/d, 3 d/week)
			12	2	10	67·0	NA	27·0	No treatment
61	Beck & Norling[92]	2010	17	2	15	68·9	NA	24·8	Ex (30 Hz, 0·3 g WBV, 15 min/d, 2 d/week)
			15	2	13	68·5	NA	26·7	Ex (12·5 Hz, 1 g WBV, 6 min/d, 2 d/week)
			15	1	14	74·2	NA	25·7	No treatment
62	Tolomio *et al.*[93]	2010	81	23	58	62·0	12·0	NA	Ex (multi-component, 60 min/d, 3 d/week)
			79	12	67	64·0	14·0	NA	No treatment
63	Yoo *et al.*[94]	2010	14	3	11	70·9	16·5	26·6	Ex (walking + ankle weights, 60 min/d, 3 d/week)
			14	4	10	71·1	16·6	25·4	No treatment
64	Chailurkit *et al.*[95]	2010	201	26	175	65·9	NA	25·2	Ca (500 mg/d)
			196	35	161	65·7	NA	25·6	Placebo
65	Kärkkäinen *et al.*[96]	2010	313	7	306	67·4	18·1	27·5	Ca (500 mg/d) + D (10 μg/d)
			290	3	287	67·4	18·1	27·4	No treatment
66	Verschueren *et al.*[97]	2011	27	2	25	80·3	NA	27·5	WBV (15 min/d, 3 d/week) + D_3 (40 μg/d) + Ca(1000 mg/d)
			29	4	25	79·8	NA	26·4	WBV (15 min/d, 3 d/week) + D_3 (22 μg/d) + Ca (1000 mg/d)
			29	2	27	78·7	NA	27·5	D_3 (40 μg/d) + Ca (1000 mg/d)
			28	2	26	79·6	NA	27·4	D_3 (22 μg/d) + Ca (1000 mg/d)
67	Choquette *et al.*[98]	2011	23	7	16	61·0	8·0	30·2	Iso (70 mg/d) + Ex (resistance + aerobic 60 min/d, 3 d/week)
			26	3	23	58·0	9·0	29·2	Iso (70 mg/d)
			26	4	22	59·0	10·0	31·0	Placebo
68	Marques *et al.*[99]	2011	30	3	27	70·1	13·3	28·4	Ex (multi-component, 60 min/d, 2 d/week)
			30	8	22	68·2	12·7	28·2	No treatment
69	Marques *et al.*[100]	2011	23	8	15	67·3	13·3	28·8	Ex (resistance, 60 min/d, 3 d/week)
			24	5	19	70·3	13·7	27·5	Ex (aerobic, 60 min/d, 3 d/week)
			24	4	20	67·9	12·8	28·1	No treatment
70	Tartibian *et al.*[101]	2011	20	NA	NA	61·4	NA	25·1	Ex (aerobic, walking, jogging, 25–45 min/d, 3–6 d/week)
			18	NA	NA	58·9	NA	28·5	No treatment
71	Je *et al.*[102]	2011	40	13	27	68·1	18·4	23·8	K_2 (45 mg/d) + Ca (630 mg/d) + D (10 μg/d)
			38	20	18	67·6	16·8	24·5	Ca (630 mg/d) + D (10 μg/d)
72	Karakiriou *et al.*[103]	2012	10	NA	NA	53·4	4·8	28·1	Ex (aerobic + resistance, 3 d/week)
			13	NA	NA	53·4	5·1	27·3	Ex (WBV, 7–12 min/d, 3 d/week)
			9	NA	NA	53·0	3·5	30·5	No treatment
73	Macdonald *et al.*[104]	2013	101	11	90	64·9	NA	25·2	D_3 (25 μg/d)
			102	18	84	64·2	NA	25·3	D_3 (10 μg/d)
			102	12	90	64·6	NA	25·9	Placebo
74	Basat *et al.*[105]	2013	14	3	11	55·9	13·3	25·0	Ex (strengthening, 60 min/d, 3 d/week)
			14	2	12	55·6	13·1	26·4	Ex (high impact, 60 min/d, 3 d/week)
			14	2	12	56·2	12·8	27·5	No treatment

Table 2. (*Continued*)

	Authors	Publication year	Baseline *n*	Loss *n*	Final *n*	Age (years)	YSM	BMI (kg/m^2)	Intervention
75	Chilibeck *et al.*[106]	2013	87	15	72	55·8	NA	NA	Ex (strength + walking) + Iso (165 mg/d) + Ca (1200 mg/d) + D (20 μg/d)
			86	9	77	55·3	NA	NA	Ex (strength + walking) + Ca (1200 mg/d) + D (20 μg/d)
76	Rajatanavin *et al.*[107]	2013	204	26	178	66·0	16·7	25·2	Ca (500 mg/d)
			200	35	165	65·6	16·1	25·6	Placebo
77	Lai *et al.*[108]	2013	16	2	14	60·1	9·8	22·7	Ex (WBV, 5 min/d, 3 d/week)
			16	2	14	62·4	10·6	23·1	No treatment
78	Leung *et al.*[109]	2014	364	84	280	74·2	24·7	24·1	Ex (WBV, 20 min/d, 5 d/week)
			346	30	316	71·0	21·5	24·0	No treatment
79	Jiang *et al.*[110]	2014	118	10	108	64·6	15·1	NA	K_2 (45 mg/d) + Ca (500 mg/d)
			118	13	105	64·2	15·6	NA	D (α-calcidol 0·5 μg/d) + Ca (500 mg/d)
80	Koitaya *et al.*[111]	2014	24	0	24	58·3	7·8	22·0	K_2 (1·5 mg/d)
			24	0	24	58·5	6·8	21·8	Placebo
81	Moreira *et al.*[112]	2014	64	5	59	58·6	NA	NA	Ex (aquatic 3 d/week, 50–60 min/d) + Ca (500 mg/d) + D (25 μg/d)
			44	3	41	59·3	NA	NA	Ca (500 mg/d) + D (25 μg/d)
82	Nicholson *et al.*[113]	2015	28	4	24	66·0	NA	26·0	Ex (pump, 50 min/d, 2 d/week)
			29	3	26	65·6	NA	24·5	No treatment
83	Santin-Medeiros *et al.*[114]	2015	25	6	19	82·3	NA	NA	Ex (WBV, x min/d, 2 d/week)
			18	0	18	82·2	NA	NA	No treatment
84	Tankisheva *et al.*[115]	2015	17	2	15	75·7	NA	29·3	Ex (vibration, 60 min/d, 5 d/week)
			18	2	16	77·6	NA	26·1	No treatment
85	Wang *et al.*[116]	2015	40	3	37	57·9	NA	NA	Ex (Tai Chi resistance training, 60 min/d, 4 d/week)
			40	6	44	58·5	NA	NA	Ex (traditional Tai Chi, 60 min/d, 4 d/week)
			39	4	35	58·5	NA	NA	No treatment
86	Wen *et al.*[117]	2017	24	0	24	57·5	7·3	21·7	Ex (step aerobics, 90 min/d, 3 d/week)
			24	2	22	58·8	4·6	22·3	No treatment
87	Shin *et al.*[118]	2018	14	1	13	55·8	7·5	24·6	Ex (WBV with load stimulation, 5 d/week)
			14	1	13	57·2	9·1	23·9	Ex (WBV, 5 d/week)
			13	2	11	54·6	7·1	25·0	No treatment
88	de Oliveira *et al.*[119]	2018	17	0	17	56·4	8·8	26·2	Ex (vibration, 5 min/d, 3 d/week)
			17	0	17	55·6	8·4	27·2	Ex (pilates, 60 min/d, 3 d/week)
			17	0	17	54·1	9·1	27·3	No treatment
89	Aboarrage Junior *et al.*[120]	2018	NA	NA	15	NA	NA	30·0	Ex (30 min/d, 3 d/week)
			NA	NA	10	NA	NA	27·0	No treatment
90	Bislev *et al.*[121]	2018	40	0	40	NA	NA	27·7	VD_3 (70 μg/d)
			41	0	41	NA	NA	26·6	Placebo

YSM, years since menopause; NA, not available; Ex, exercise; D, vitamin D; Est, oestrogen; PEPI, Postmenopausal Estrogen/Progestin Interventions; K, vitamin K; Iso, isoflavone; WBV, whole body vibration.
* Groups which did not meet the inclusion criteria are not shown.
† Injection.

Within the network, there are thirty-seven intervention pairs for which both direct and indirect comparisons are available. Only the comparison between Ca and placebo ($P = 0·037$) and that between Ca + vitamin D and Ca ($P = 0·031$) showed significant evidence of inconsistency (online Supplementary Fig. S4).

The overall network heterogeneity τ was 0·021, and I^2 was 95·94. The heterogeneity of each comparison is shown in online Supplementary Table S2.

Femoral neck

Network meta-analysis for the mean differences in FN BMD included fifty-five RCT (*n* 6707) with sixteen different types of interventions (Fig. 2(b)). The effects of each intervention are presented in Fig. 3(b). Ca (0·031 g/cm^2, 95 % CrI 0·0058, 0·058 g/cm^2), exercise (0·028 g/cm^2, 95 % CrI 0·014, 0·042 g/cm^2) and vitamin D + oestrogen (0·050 g/cm^2, 95 % CrI 0·0080, 0·092 g/cm^2) were associated with significant beneficial intervention effects relative to no treatment.

Within the network, both direct and indirect comparisons are available for thirty-two intervention pairs. None of them showed significant evidence of inconsistency (online Supplementary Fig. S5).

The overall heterogeneity τ was 0·019 and I^2 was 96·59 in this network. The heterogeneity of each comparison is shown in online Supplementary Table S3.

Ranking probability

As shown in Table 3, the SUCRA values demonstrated that vitamin D + oestrogen had the highest SUCRA values for change of BMD in the LS (97·29 %), followed by Ca + vitamin D and exercise (86·86 %) and oestrogen (85·70 %). Ca + exercise had the highest SUCRA values for change of BMD in the FN (79·71 %),

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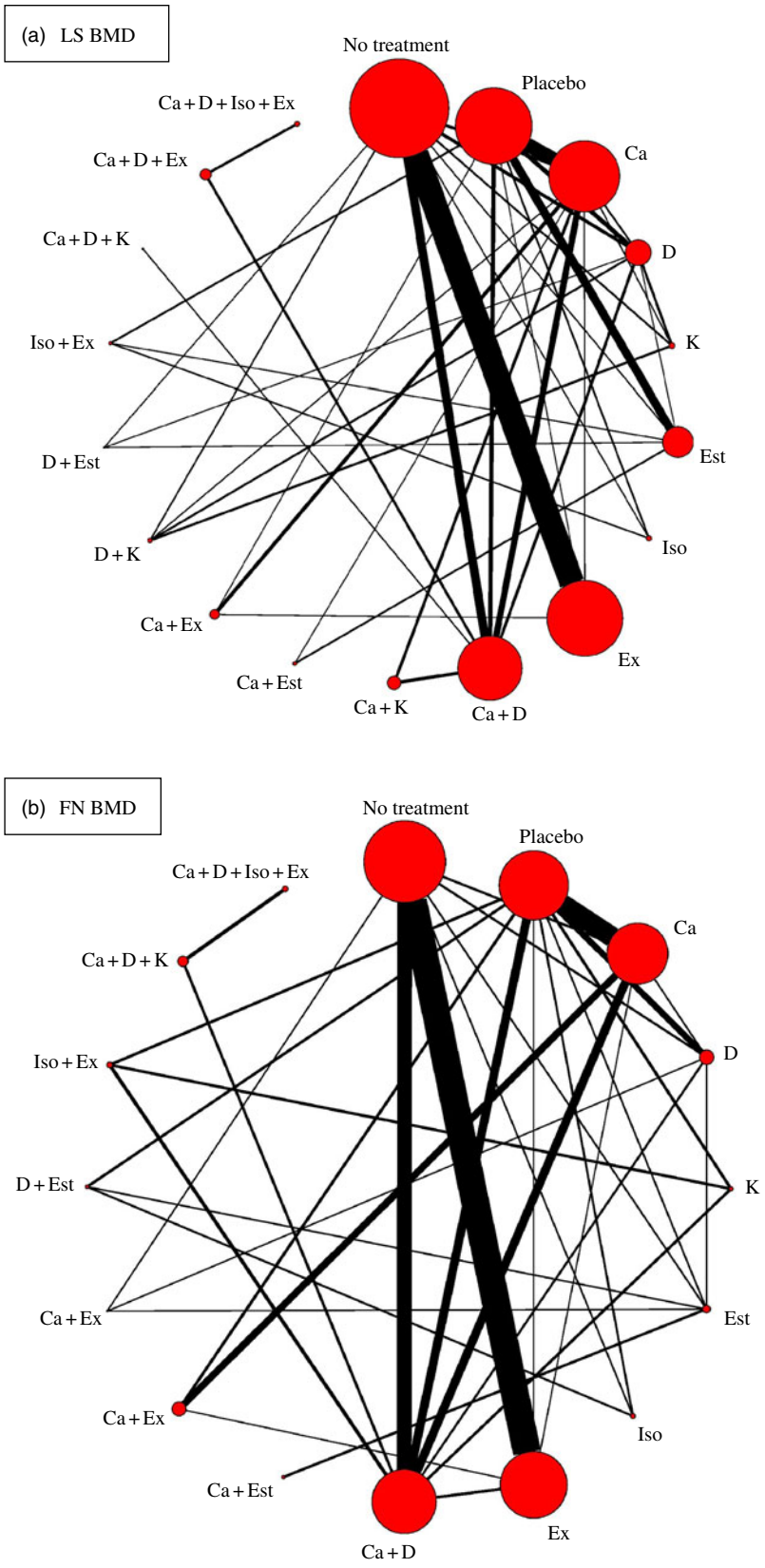

Fig. 2. (Colour online) Network plots for included studies with available direct comparisons for lumbar spine (LS) and femoral neck (FN) bone mineral density. Each node indicates an intervention and each line connecting two nodes indicates a direct comparison between two interventions. The size of the nodes and the thickness of the edges are weighted according to the number of participants evaluating each intervention and direct comparison, respectively. D, vitamin D; Est, oestrogen; Ex, exercise; K, vitamin K; Iso, isoflavone.

(a) LS BMD

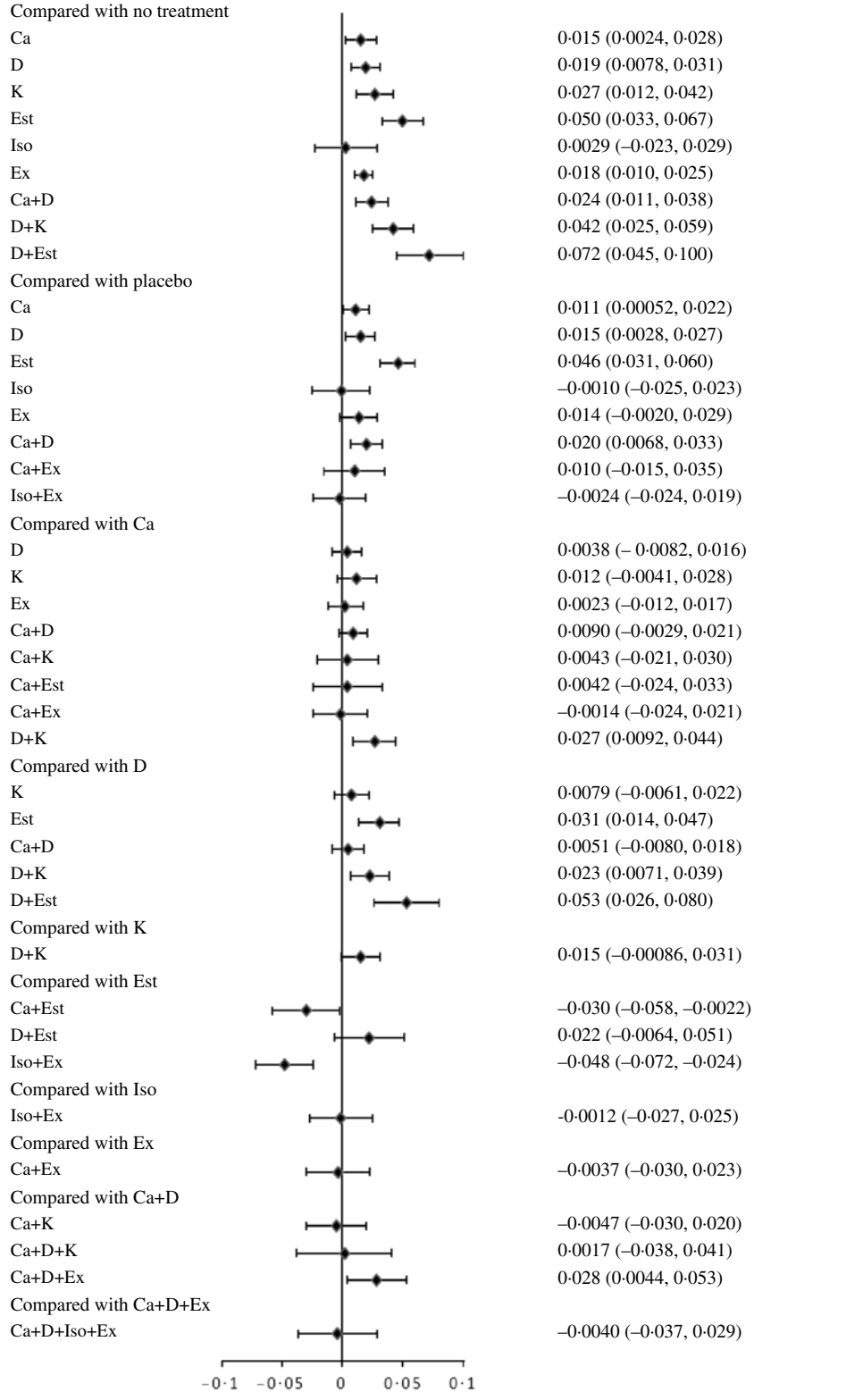

Fig. 3. Effect size for change in bone mineral density (BMD) using forest plots. LS, lumbar spine; D, vitamin D; Est, oestrogen; Ex, exercise; K, vitamin K; Iso, isoflavone; FN, femoral neck.

(b) FN BMD

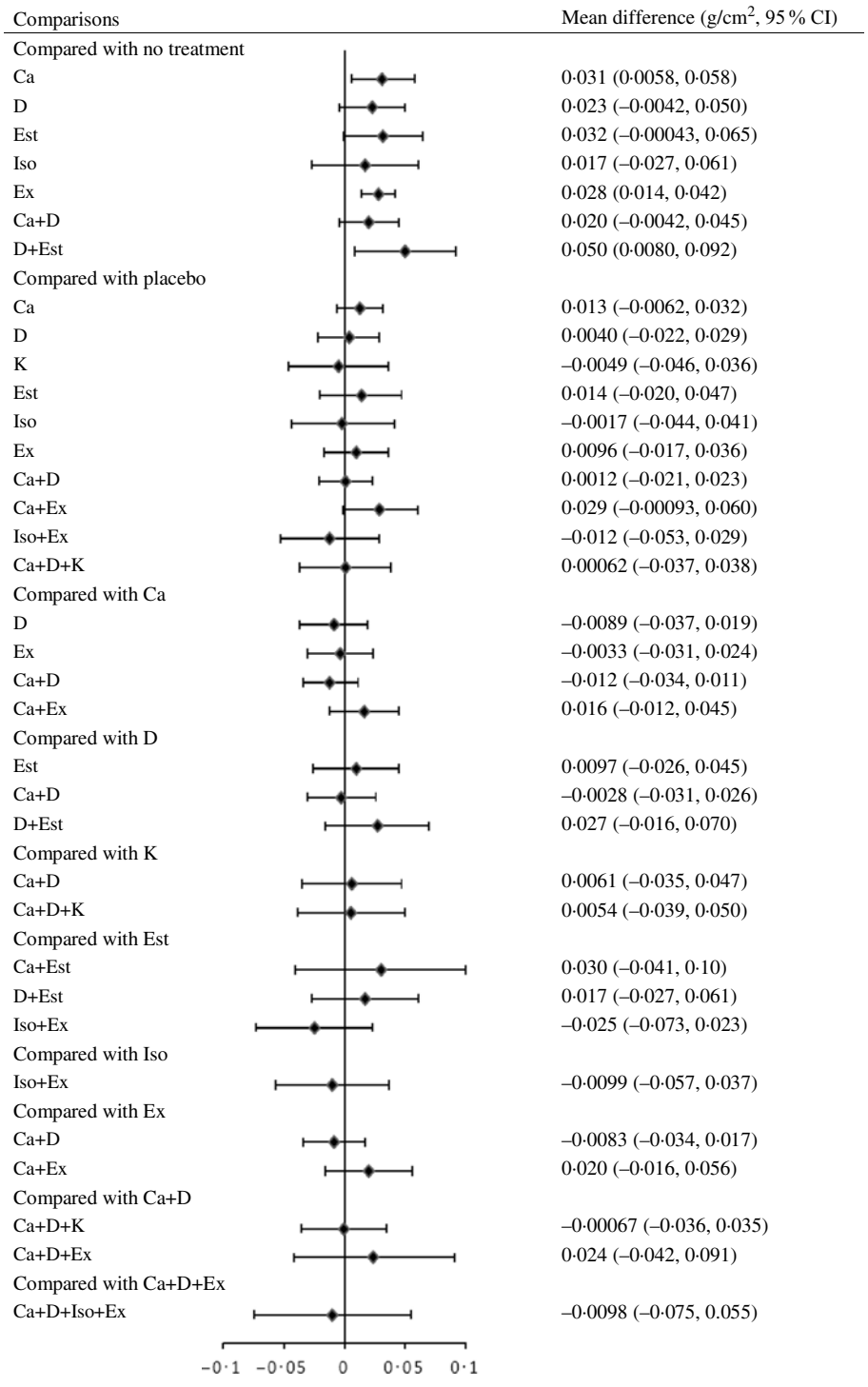

Fig. 3. Continued

followed by Ca + oestrogen (79·38 %) and vitamin D + oestrogen (78·33 %). As for single interventions, oestrogen might be the best intervention to improve BMD in the LS (85·70 %) and Ca for FN (60·58 %). Most intervention combinations had higher SUCRA values than single interventions. The details of cumulative rank probabilities are supplied in the Supplementary material (online Supplementary Tables S4 and S5).

Sensitivity analysis

The minimum and maximum correlation values between BMD at baseline and the end of the intervention used to impute missing SD of BMD change were subject to a sensitivity analysis (online Supplementary Tables S6–S9). The findings were similar to those of the primary analysis. Another sensitivity analysis was conducted using the mean difference of BMD change after 15 months of intervention, which was the average duration of intervention in the included studies (online Supplementary Tables S6–S9). For LS BMD, the ranking of exercise was higher, from 12th to 5th, Ca + vitamin D and exercise appeared to be the highest rank and the rankings of higher ranked interventions remained stable. For FN BMD, the ranking of exercise was also higher, from 8th to 4th. Other findings were similar to those of the primary analysis. The last sensitivity analysis was conducted by excluding studies with group sample size less than 15. Higher ranked interventions remained ranking high.

Table 3. Intervention rankings using surface under the cumulative ranking (SUCRA) values

	LS BMD		FN BMD	
Rank	Intervention	SUCRA (%)	Intervention	SUCRA (%)
1	D + Est	97·29	Ca + Ex	79·71
2	Ca + D + Ex	86·86	Ca + Est	79·38
3	Est	85·70	D + Est	78·33
4	Ca + D + Iso + Ex	79·54	Ca + D + Ex	67·00
5	D + K	78·95	Ca	60·58
6	K	60·04	Est	59·23
7	Ca + D	55·81	Ca + D + Iso + Ex	55·13
8	Ca + D + K	53·21	Ex	54·12
9	D	44·68	D	44·47
10	Ca + Est	44·50	Ca + D + K	40·06
11	Ca + K	44·49	Ca + D	39·47
12	Ex	41·08	Iso	37·39
13	Ca	35·98	Placebo	36·47
14	Ca + Ex	35·12	K	32·97
15	Iso	17·36	Iso + Ex	24·57
16	Placebo	15·14	No treatment	11·13
17	Iso + Ex	14·86		
18	No treatment	9·39		

LS, lumbar spine; BMD, bone mineral density; FN, femoral neck; D, vitamin D; Est, oestrogen; Ex, exercise; Iso, isoflavone; K, vitamin K.

Discussion

To our knowledge, this network meta-analysis is the first to compare the effects of various osteoporosis prevention methods on BMD in postmenopausal women, including Ca, vitamin D, vitamin K, oestrogen, isoflavone, exercise and their combinations. In this network meta-analysis, direct and indirect evidence from ninety RCT including 10 777 postmenopausal women was combined to compare the effect size of each intervention on BMD in both the LS and the FN. The results showed that compared with placebo or no treatment, many interventions can prevent bone loss. In addition, different single or combined interventions may have different impacts on different sites. However, some of the interventions had limited participants or involved limited studies, which may exaggerate or reduce the effect size of those interventions.

Ca and vitamin D supplements have long been considered as ways to prevent osteoporosis, and their effectiveness is consistent with our findings. Ca and vitamin D combined with exercise have beneficial effects on BMD in both the LS and the FN. It was found that the effect of Ca alone on FN BMD is greater than that of LS, which may be due to the different sensitivity of different sites to Ca supplementation, but the exact mechanism needs to be investigated further. Low bone density can not only cause fractures but also lead to bone pain and body metamorphosis[4]. This is the reason that BMD was chosen as the primary outcome in our study, although there has been some controversy about whether Ca and vitamin D effectively improve BMD and fracture rates[122] and Ca and vitamin D supplements may not prevent women from fracture[123]. Fracture prevention requires all-round efforts, including improving BMD, maintaining muscle strength, maintaining a sense of balance and creating a safe home[124]. Increasing BMD is important, but it is not the only component of fracture prevention.

Vitamin K plays an important role in the γ-carboxylation of osteocalcin, allowing osteocalcin to bind Ca and thus rendering it functional[125]. The effect size of vitamin K on BMD was different between the LS and the FN. Vitamin K ranked 6th among the eighteen interventions for LS but 14th among the sixteen interventions for FN, indicating that vitamin K supplementation can increase LS BMD but not FN BMD. This result is consistent with Fang's meta-analysis that assessed the effects of vitamin K on BMD[126]. Another meta-analysis showed that vitamin K_2 can improve vertebral BMD in postmenopausal women with osteoporosis, while it did not have any effect in postmenopausal women without osteoporosis[127]. The present study also showed that vitamin K_2 might have a higher adverse reaction rate than control treatment. Considering the adverse reactions and different effects on postmenopausal women with and without osteoporosis, vitamin K should be carefully chosen for osteoporosis prevention.

Oestrogen is mainly generated by the ovaries in premenopausal women. Functional decline of the ovaries after menopause reduces oestrogen secretion. Oestrogen acts on osteoblasts and osteoclasts, thus affecting bone metabolism[128]. In this network meta-analysis, oestrogen + vitamin D was demonstrated to be the most effective way to improve LS BMD, and oestrogen + Ca was the most effective way to improve FN BMD. Oestrogen alone can be effective as well, a similar result to those of previous studies[129]. There were no interventions of oestrogen + Ca or vitamin D in our study, so the effects of these combinations remain unknown. If such studies are conducted in the future, this analysis can be updated. A previous meta-analysis showed that hormone replacement therapy (including oestrogen and progesterone) has a consistent, favourable, and large effect on bone density at all sites[130]. However, considering

the possible side effects of oestrogen and the limitations of access to oestrogen[131], it should be taken under the guidance of a physician.

Isoflavone is a compound that has oestrogen-like activity in plants, and it exerts a weak oestrogenic effect by binding to the oestrogen receptor[132]. It is still unknown whether its mechanism of action on bone turnover is the same as that of oestrogen[133]. Isoflavone (not soya protein or foods containing isoflavone) was found to have a very limited effect on BMD in both the LS and the FN in the present study. Many studies, even meta-analyses, have shown inconsistent results about the role of isoflavone on BMD. In Taku's meta-analysis, soya isoflavone extract supplements were found to have no effects on FN, total hip or trochanter BMD in menopausal women, and they concluded that it can only increase LS BMD[134]. Ricci's meta-analysis reported that isoflavone mixtures cannot decrease bone loss in perimenopausal and postmenopausal western women[135]. Another two meta-analyses showed that lower doses were not effective at increasing BMD, while intake of more than 80–90 mg/d tended to have a beneficial effect[136,137]. The effect of isoflavone on BMD is limited, but one study demonstrated that isoflavone may be safer than hormonal therapy for prevention of bone loss in postmenopausal women[138].

Exercise was shown to improve BMD to a certain extent in our study. The benefits of exercise lie not only in increasing BMD but also in improving muscle strength to prevent falling. Many meta-analyses have been conducted on different kinds of exercise. Kelley's studies reported that aerobic exercise had a moderately positive effect on BMD in both the LS and the FN[139,140], while resistance exercise did not maintain or improve BMD in either the LS or the FN[141]. Most studies have suggested that combined exercise interventions effectively preserve postmenopausal women's BMD[142]. Some meta-analyses have also suggested that exercise did not improve BMD in the FN[143]. The studies may have had different results because of the different exercise protocols they used. In our study, exercise + Ca and vitamin D effectively prevented BMD loss. Exercise, as an intervention that can contribute to many other chronic non-communicable diseases in older people[144], is worthy of wide promotion.

Although there was high statistical heterogeneity indicated by I^2 in this network, it may be due to the large sample size in the study. The τ, which is independent of the study sample size, indicated low between-study heterogeneity. What is more, a node-splitting model was used to assess the potential inconsistency. Three other sensitivity analyses were conducted, which produced stable, consistent results. BMI, as a potential effect modifier, is generally thought to have a positive correlation with BMD[145]. However, study also indicated that BMI was not a determinant of BMD in postmenopausal women in an Asian population. What is more, mean differences in BMD were used to minimise the impact of baseline BMI in our study.

Limitations

The present study has several limitations. First, we did not conduct subgroup analyses of women with different YSM, BMI or osteoporosis status to define the best intervention methods for women with varying YSM, BMI and BMD. These information were not available from all included studies. Moreover, each type of intervention was combined into a single category, which makes it impossible to distinguish between high and low dosages or between slightly different forms of intervention (e.g. vitamin D_2 *v.* D_3, aerobic *v.* resistant exercise). The purpose of our research was to compare different kinds of interventions. Further studies should explore the effect sizes of different dosages and interventions in a network meta-analysis.

Second, we only included studies that employed oestrogen intervention and excluded studies that employed progesterone or androgens (such as hormone replacement therapy and tibolone), because it is unknown whether the effects of oestrogen on BMD will change if combined with progesterone or androgens. However, one study demonstrated that the effect size on BMD does not differ between tibolone and any oestrogen compound[146]. Progesterone can prevent endometrial hyperplasia during long-term oestradiol replacement[147]. If oestrogen is used to prevent postmenopausal osteoporosis, physicians' guidance is necessary according to individual circumstances to decide the dosage and use of progesterone and androgens.

Third, the gemtc package is currently the most suitable package for analysing our study's data. However, because of the limitations of the package, not all results of the comparisons between each pair of interventions were shown in the network forest plot, such as Ca + oestrogen compared with no treatment or placebo. Thus, mean differences were used to define if there was an effect or not in our study because some 95 % CrI of the effect sizes were not available.

Conclusion

The present study demonstrated that many interventions were valuable for improving BMD in the LS and FN of postmenopausal women. It confirmed the need for postmenopausal women to improve BMD through preventive measures such as nutrients or oestrogen. It also confirmed that different single or combined preventions can affect BMD at different sites in different orders. This reveals to medical and health workers and postmenopausal women which methods can be selected preferentially to prevent bone loss.

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Z. X., H. W., Y. S., Q. S., L. T., Z. W. and Y. C. designed and conducted the study. Z. X. and H. W. analysed the data. All authors participated in the interpretation of data. Z. X. drafted the manuscript. All authors helped to revise the manuscript and accept this version for publication. Y. C. is the supervisor.

There are no conflicts of interest.

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Supplementary material

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