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Systematic Review

Role of calcium &/or vitamin D supplementation in preventing osteoporotic fracture in the elderly: A systematic review & meta-analysis

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***Background & objectives*: Calcium and vitamin D, separately or in combination are usually prescribed to prevent fragility fractures in elderly population. However, there are conflicting results regarding the ideal dosage and overall efficacy obtained from randomized controlled trials (RCTs) conducted in the past. The objective of this study was to assess the fracture risk with the administration of calcium or vitamin D alone or in combination in elderly population (>60 yr).**

***Methods*: PubMed, Cochrane and Embase databases were searched to identify the studies from inception to February 2021 with keywords, 'vitamin D', 'calcium' and 'fracture' to identify RCTs. The trials with comparing vitamin D, calcium or combination with either no medication or placebo were included for final analyses. The data were extracted and the study quality was assessed by two reviewers. The principal outcome measure was fractures around hip joint and secondary outcomes assessed were vertebral and any other fracture.**

***Results*: Eighteen RCTs were considered for the final analysis. Neither calcium nor vitamin D supplementation was associated with risk of fractures around hip joint [risk ratio (RR) 1.56; 95% confidence interval (CI), 0.91 to 2.69, I^2=28%; *P*=0.11]. In addition, the combined administration of calcium and vitamin D was also not associated with fractures around the hip joint in comparison to either no treatment or placebo. The incidence of vertebral (RR 0.95; 95% CI, 0.82 to 1.10, I^2=0%; *P*=0.49) or any other fracture (RR 0.83; 95% CI 0.65 to 1.06, I^2=0%; *P*=0.14) was not significantly associated with the administration of calcium and vitamin D either individually or in combination. Further subgroup analysis of the results did not vary with the dosage of calcium or vitamin D, dietary calcium intake sex, or serum 25-hydroxyvitamin D levels.**

***Interpretation & conclusions*: The present meta-analysis of RCTs on calcium, vitamin D or a combination of the two in comparison to no treatment or placebo did not support the routine administration protocol of calcium and vitamin D either alone or in combination to lower the risk of fractures in elderly population.**

Key words 25-Hydroxyvitamin D - calcium - hip fracture - osteoporosis - risk - randomized controlled trials - vitamin D

With the rise in the elderly population worldwide, the incidence of osteoporotic fractures is increasing proportionately[1]. Reportedly, there is a probability that approximately 50 per cent women and 20 per cent men aged 50 yr suffer an osteoporotic fracture in their remaining lifetime[2,3]. Hip fracture is one among the most serious types of fragility fractures with approximately one third risk of death in the subsequent year[4]. The survivors require good nursing and social care which translates into a major social and economic burden[5]. Hence, the thrust should be on prevention of these fractures. Common practice is to recommend combined calcium and vitamin D supplements to patients after an osteoporotic fracture to prevent chances of the same in the future. Vitamin D is required for the maintenance of good musculoskeletal health as it promotes the absorption of calcium, osteoid mineralization and maintenance of muscle functions.

Previous studies on the effect of calcium supplementation on bone density have demonstrated that there is no substantial increase in bone density beyond one year of calcium administration[6,7]. Moreover, the influx of calcium ions in the blood leads to suppression in the parathyroid hormone levels, thus affecting the cycle of bone resorption and formation[8]. Few observational studies in the past have also shown that there is no relationship between calcium intake and risk of fracture[9]. The regions with low calcium intake touching Asia and Africa have a lower incidence of fracture in comparison to Europe and North America. This phenomenon has been referred to as the 'Calcium Paradox'. In published literature, there is no consensus to support the use of either calcium alone or in combination with vitamin D to reduce the risk of subsequent fractures. Hence, this meta-analysis was planned to assess calcium and, vitamin D individually or in combination administration of calcium and vitamin D with placebo for fracture incidence in the elderly population.

Material & Methods

This systematic review and meta-analysis was performed as per the recommendations of the PRISMA statement[10] and was registered in PROSPERO (CRD 42021218539).

Search strategy: PubMed, EMBASE and COCHRANE databases were searched since inception to February 2021, to collect information on published trials for evaluating the association between calcium and, vitamin D (individually or in combination) supplementation on the incidence of fractures in elderly individuals with a prior history of a fracture. In addition, *clinicaltrials.gov* was also searched for any undergoing trials. The keywords searched were 'calcium', 'vitamin D', and 'fracture'. No restriction of language, date or publication status was applied on the search. The bibliographic details of all the included studies were searched manually for any additional citations. In case of duplication of publication, the study with the entire data set was excluded. The complete search strategy has been listed in the Supplementary Material.

Inclusion criteria: Randomized controlled trials (RCTs) or meta-analyses comparing calcium, and vitamin D, individually or in or combination administered either with placebo or no treatment were included in this study. Furthermore, this studies included adults older than 50 yr with a previous history of fracture.

Exclusion criteria: Studies without a treatment or placebo group, with individuals having glucocorticoid-associated osteoporosis, employed co-administration of calcium and, vitamin D individually or in combination with other treatment modalities like antiresorptive medication or included of dietary supplementation of either calcium or vitamin D were excluded from this study.

Selection of study data and data extraction: All the studies were independently screened for meeting the study criteria using Rayyan web application[11]. In case of any disagreement regarding the inclusion of the study, the matter was resolved by a third author. The reviewers independently extracted the characteristics of the studies and outcome measures. The extraction form was developed as per Cochrane recommendations[12]. Any discrepancy between the data extracted twice was resolved by analysis of the full text by all the reviewers. The patient characteristics, calcium and, vitamin D administered individually or in combination, dicalcium intake, serum vitamin D levels, cases with a history of hip, vertebral or non-vertebral fracture along with the duration of the trial were recorded.

Assessment of risk of bias: Cochrane Collaboration's tool was used to check for the quality of studies included for the meta-analysis[13]. Each study was checked for random generation of sequence; reporting of selective outcome; concealment of allocation; blinding of participants; incomplete outcome data; selective outcome reporting and potential sources of bias like

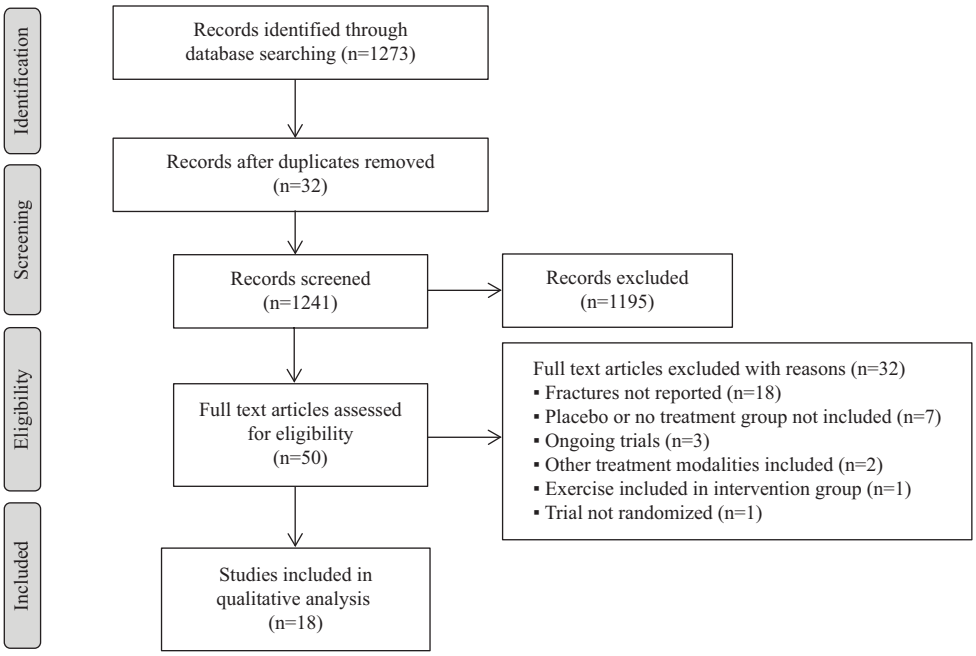

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the study inclusion and exclusion procedure.

conflicts of interest. The performance of each study was checked for risk of bias and tabulated. The risk of bias was categorized as low, medium and high risk. When either randomization or allocation concealment was assessed as a high risk of bias regardless of other items, the trials were considered as low quality. Similarly, when both randomization and allocation concealment was assessed as a low risk of bias and other items as low or unclear risk of bias, the trial was considered as high quality. The trials which did not meet high or low quality criteria were considered as moderate quality[14,15]. A study was labelled with low risk of bias if six out of the seven chosen domains were found to be low risk[12].

Statistical analysis: The incidence of fracture was assessed for association with calcium and, vitamin D, administration individually or in combination. Each component was also compared with a placebo or treatment given in the studies. The meta-analysis was performed to obtain relative risk ratios, absolute risk difference and 95% confidence interval. In cases where relative risk and absolute risk difference lead to similar end result, the results of relative risk were taken into consideration, especially when an intervention was targeted to prevent an unwanted event[16].

The random-effect model of derSimonian and Laird approach[17] was used to estimate pooled RRs and mean differences with the inverse variance approach. In case of no event in a group, the RR was estimated by adding 0.5 to each cell. The testing of heterogeneity was carried out using Chi-squared test and quantified using I^2. In the case of I^2>50 per cent, substantial heterogeneity was considered. P<0.10 was considered significant.

To evaluate the association of fracture with the variables under interest, the subgroups were specified based on dosage with the frequency of calcium supplementation, sex, dietary intake and baseline serum vitamin D levels. The subgroups were analyzed to look for significant results (P<0.05). Funnel plots were used to assess publication bias when the number of trials reporting the primary outcomes was ≥10. The statistical analyses were performed using Review Manager Software (Cochrane Collaboration, UK). The criteria mentioned in Cochrane Handbook were used to convert medians, standard errors and 95 per cent CI to means and standard deviations.

Results

Literature search: A total of 1273 articles were obtained in the initial search for published RCTs on the study topic. Of these, 32 duplicate articles were removed, leaving 1241 for screening. After screening titles and abstracts, 46 full text articles remained for review and 18 articles were included as per the criteria. Hence, a

Table I. Characteristics of included randomized controlled trials and participants

Study	Country	Total number of participants	Male:female ratio	Intervention	Comparator	Mean age (yr)	Calcium intake (mg/day)	Serum vitamin D
Hansson and Roos *et al*[18], 1987	Sweden	50	0:50	1 g/d calcium (n=25)	Placebo (n=25)	65.9	NA	NA
Reid *et al*[19], 1993	New Zealand	135	0:135	1 g/d calcium (n=25)	Placebo (n=67)	58	750	37.5
Recker *et al*[20], 1996	United States	197	0:197	1.2 g/d calcium (n=135)	Placebo (n=102)	73.5	434	25.5
Peacock *et al*[21], 2000	United States	261	74:187	0.75 g/d (n=126)	Placebo (n=102)	73.8	597	25
Avenell *et al*[22], 2004	United States	105	53:11	1 g/d calcium (n=35); 800 IU/day	No treatment (n=35)	78	NA	NA
Harwood *et al*[23], 2004	United Kingdom	75	0:75	3,000,000 IU single dose (n=38)	No treatment (n=37)	80.5	NA	11.6
Porthouse *et al*[24], 2005	United Kingdom	3314	0:3314	1 g/d calcium (n=1321); 800 IU/day	No treatment (n=1993)	76.8	1080	NA
Grant *et al*[25], 2005	United Kingdom	2643	402:2241	1 g/d calcium (n=1311); 800 IU/day	Placebo (n=1332)	77	NA	15.2
Prince *et al*[26], 2006	Australia	1460	0:1460	0.48 g/d calcium (n=730)	Placebo (n=730)	75.2	915	31
Reid *et al*[27], 2006	New Zealand	1471	0:1471	1 g/d calcium (n=732)	Placebo (n=739)	74.3	857	20.7
Jackson *et al*[28], 2006	United States	7972	0:7972	1 g/d calcium (n=4015); 400 IU/day	Placebo (n=3957)	62.4	1151	18.9
Smith *et al*[29], 2007	United Kingdom	9440	4354:5086	3,000,000 IU single dose (n=4727)	Placebo (n=4713)	79.1	625	22.6
Sander's *et al*[30], 2010	Australia	2258	0:2258	5,000,000 IU every year (n=1131)	Placebo (n=1127)	76.1	976	19.8
Salvovaara *et al*[31], 2010	Finland	3432	0:3432	1 g/d calcium (n=1718); 800 IU/day	No treatment (n=1714)	67.3	957	19.8
Punthakee *et al*[32], 2012	Canada	1221	722:499	1000 IU/day (n=607)	Placebo (n=614)	66.6	NA	NA
Hin *et al*[33], 2017	United Kingdom	305	155:150	4000 IU/day (n=102); 2000 IU/day (n=102)	Placebo (n=101)	71.7	710	20.1
Khaw *et al*[34], 2017	New Zealand	5108	2969:2139	2,000,000 IU single dose followed by 1,00,000 monthly (n=2558)	Placebo (n=2550)	65.9	810	25.2
Xue *et al*[35], 2017	China	312	0:312	0.6 g/d calcium (n=139); 800 IU/day	Placebo (n=173)	63.6	NA	30.8

NA, not available

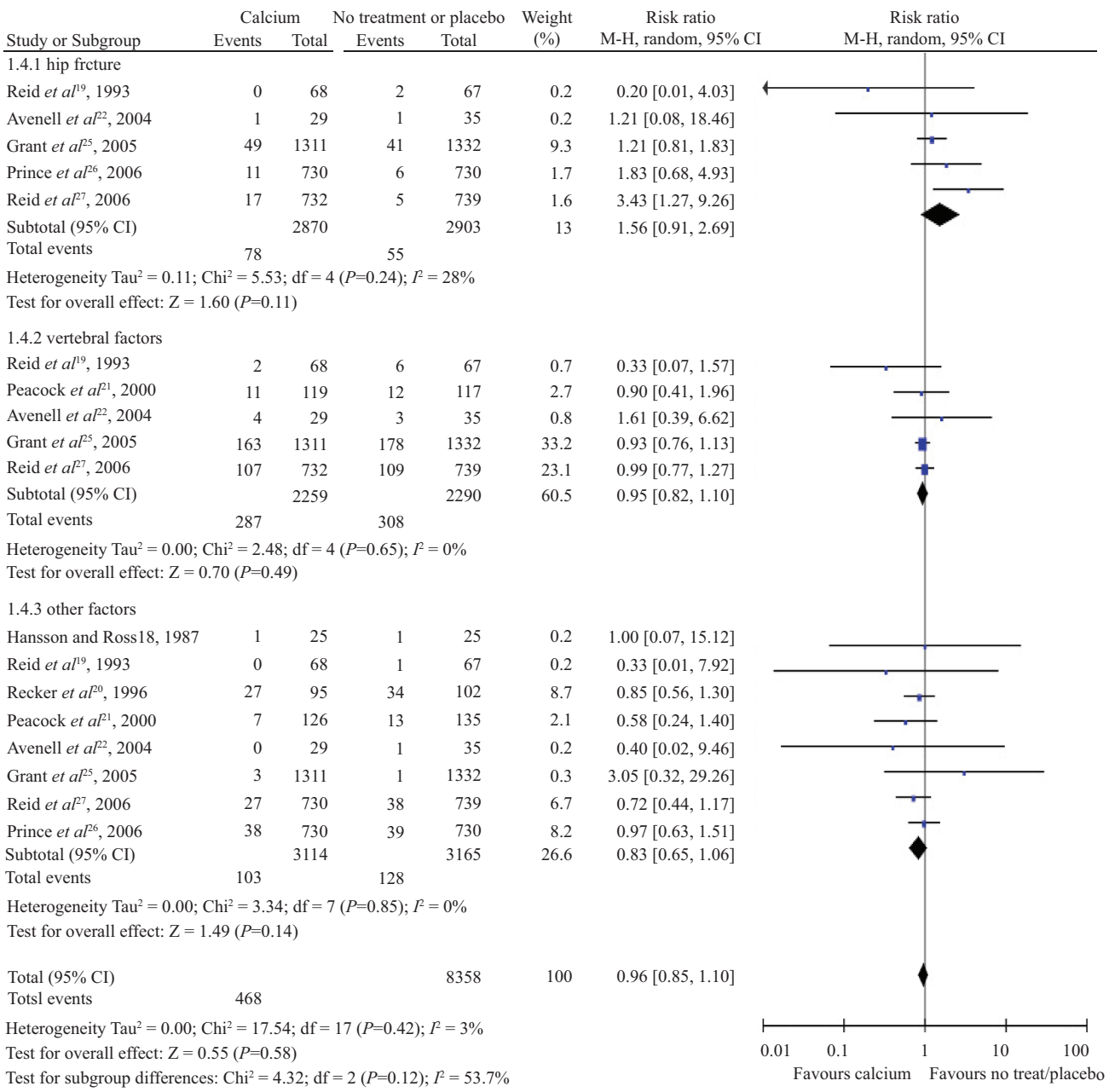

Fig. 2. Forrest plot of trials with administration of calcium for prevention of fracture in hip, vertebrae and other parts of the body.

total of 18 RCTs which involved 39759 participants were selected in this meta-analysis (Fig. 1). The characteristics of the included RCTs are given in Table I and the list of excluded trials along with the reasons have been provided in the Supplementary Table.

The risk of bias of the studies included was assessed (Supplementary Figs 1 and 2). Egger's linear regression analysis was used for the evaluation of publication bias for the primary outcome measure and no publication bias was noted (*P*=0.901; Supplementary Fig. 3).

Calcium intake and risk of fracture: Calcium was administered in the form of calcium carbonate in ten trials, calcium citrate malate in two trials, calcium citrate in two trials; combination of bicarbonate, lactate and, gluconate in one trial; lactate, gluconate, carbonate in two trials and unclear form in one trial. The association between calcium administration and hip fracture [risk ratio (RR) 1.56; 95% confidence interval (CI), 0.91 to 2.69, I^2=28%; *P*=0.11], vertebral fracture (RR 0.95; 95% CI, 0.82 to 1.10, I^2=0%; *P*=0.49) or

Table II. Subgroup analysis for calcium administration and fracture risk prevention in each factor

Factor	Participants with fracture	Total number of participants	RR (95% CI)	*P*
Hip fracture				
Dose of calcium				
<1 g	17	1460	1.83 (0.68-4.93)	0.76
>1 g	116	4313	1.51 (0.67-3.37)	
Sex				
Women only	41	3066	1.97 (0.74-5.28)	0.31
Both sex	92	2707	1.21 (0.81-1.82)	
Serum 25(OH)D levels at presentation				
>20 ng/ml	41	3066	1.97 (0.74-5.28)	0.16
<20 ng/ml	92	2707	1.21 (0.81-1.82)	
Vertebral fracture				
Dose of calcium				
>1 g	572	4313	0.95 (0.82-1.11)	0.63
<1 g	23	236	0.90 (0.41-1.96)	
Sex				
Women only	224	1606	0.76 (0.30-1.92)	0.94
Both sex	371	2943	0.94 (0.78-1.13)	
Serum 25(OH)D levels at presentation				
>20 ng/ml	247	1842	0.96 (0.76-1.21)	0.76
<20 ng/ml	341	2643	0.93 (0.76-1.13)	
Other fracture				
Dose of calcium				
>1 g	158	1918	0.87 (0.65-1.15)	0.56
<1 g	73	4361	0.75 (0.47-1.18)	
Sex				
Women only	204	3261	0.85 (0.66-1.09)	0.97
Both sex	28	3153	0.68 (0.32-1.44)	
Serum 25(OH)D levels at presentation				
>20 ng/ml	143	3064	0.84 (0.61-1.16)	0.84
<20 ng/ml	85	3101	0.82 (0.57-1.20)	

25(OH)D, 25-hydroxy vitamin D; CI, confidence interval; RR, relative risk

other fractures (RR 0.83; 95% CI 0.65 to 1.06, I^2=0%; *P*=0.14) was not significant (Fig. 2) in comparison to either no treatment or placebo administration. The subgroup analysis was carried out for the assessment of fracture risk in the hip, vertebra and other parts of the body, but there was no significant association based on calcium dosage, sex and serum 25-hydroxy vitamin D [25OH)D] levels (Table II).

Vitamin D intake and risk of fracture: Vitamin D supplementation with a placebo or no treatment was compared in six trials. The association between vertebral fracture (RR, 1.28; 95% CI, 0.80 to 2.05, I^2=0%; *P*=0.31), hip fracture (RR, 1.18; 95% CI, 0.91 to 1.53, I^2=0%; *P*=0.21), or other fracture (RR, 1.09; 95% CI, 0.94 to 1.20, I^2=0%; *P*=0.11; Fig. 3) was not found to be significant. The subgroup analysis for different dosage and frequency of assessment of fracture risk was not found to be significantly associated (Table III).

Combined vitamin D and Calcium administration and fracture risk: Supplementation of calcium and

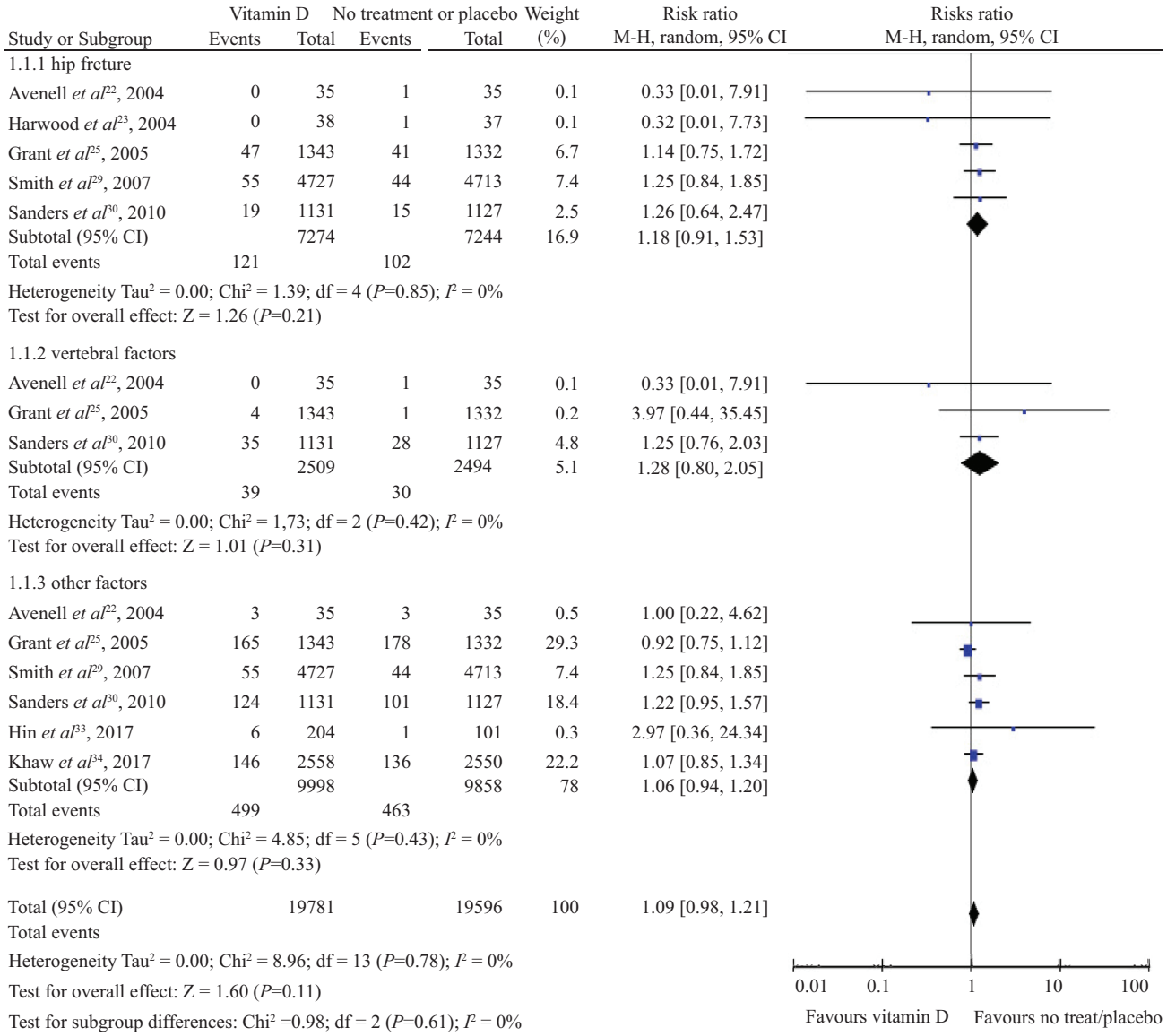

Fig. 3. Forrest plot of trials with the administration of vitamin D for prevention of fracture in hip, vertebrae and other parts of the body.

vitamin D combined versus placebo or no treatment was compared in seven trials. The association between vertebral fracture (RR, 0.63; 95% CI, 0.29 to 1.40, I^2=0%; *P*=0.26), hip fracture (RR, 1.10; 95% CI, 0.86 to 1.40, I^2=0%; *P*=0.47) and other fractures (RR, 0.921; 95% CI, 0.78 to 1.08, I^2=0%; *P*=0.29; Fig. 4) was not found to be significant. There was no significant difference in the subgroup analysis based on intake of calcium and vitamin D, sex, baseline 25(OH)D levels and dietary intake of calcium (Table IV).

Discussion

The meta-analysis revealed that calcium and, vitamin D individually or in combination did not lower the chances of hip, vertebral or any other fragility fractures in the elderly population. The exclusion of low-quality trials and trials with patients using specific medication did not affect the results. The outcome was independent of calcium, vitamin D dosage or the combination of two, sex and serum 25(OH)D levels.

Prior meta-analysis carried out by Tang *et al*[36] had reported decrease in fragility fractures with calcium supplementation. However, they had included two cluster trials[15,16] with a large sample size and did not adjust for the cases which could have increased the chance of achieving low *P* value

Table III. Subgroup analysis for vitamin D administration and fracture risk prevention in each factor

Factor	Participants with fracture	Total number of participants	RR (95% CI)	*P*
Hip fracture				
Frequency of vitamin D supplementation				
Low daily dose	89	2745	1.11 (0.74-1.68)	0.17
High dose once yearly	35	2333	1.19 (0.62-2.3)	
High dose intermittently	99	9440	1.25 (0.84-1.85)	
Sex				
Women only	34	2258	1.26 (0.64-2.47)	0.52
Both sex	89	2745	1.11 (0.74-1.68)	
Serum 25(OH)D levels at presentation				
>20 ng/ml	222	14,448	1.19 (0.92-1.55)	NA
<20 ng/ml	0	0	NA	
Vertebral fracture				
Frequency of vitamin D supplementation				
Low daily dose	6	2745	1.51 (0.14-16.14)	0.21
Intermittent high dose	63	2258	1.25 (0.76-2.03)	
Sex				
Women only	63	2258	1.25 (0.76-2.03)	0.49
Both sex	6	2745	1.51 (0.14-16.14)	
Serum 25(OH)D levels at presentation				
>20 ng/ml	0	0	NA	NA
<20 ng/ml	69	5003	1.28 (0.80-2.05)	
Other fracture				
Frequency of vitamin D supplementation				
Low daily dose	349	2745	0.92 (0.76-1.12)	0.23
High dose once yearly	225	2258	1.22 (0.95-1.57)	
High dose intermittently	282	5108	1.07 (0.85-1.34)	
Sex				
Women only	225	2258	1.22 (0.95-1.57)	0.56
Both sex	730	17,293	1.01 (0.88-1.16)	
Serum 25(OH)D levels at presentation				
>20 ng/ml	955	19551	1.09 (0.98-1.21)	NA
<20 ng/ml	0	0	NA	

CI, confidence interval; NA, not available; RR, relative risk

and narrow confidence intervals in the comparison groups. In another meta-analysis by Bolland *et al*[9], the dietary intake of calcium did not decrease the risk of fracture, and role of calcium supplementation in the prevention of fracture was also doubtful. In the present study, no association between calcium supplementation and the risk of fracture was observed. Hence, calcium supplementation need not be a routine recommendation for lowering risk of fracture.

A meta-analysis by Bischoff-Ferrari *et al*[37] had reported lower chances of hip fracture and other fragility fractures with the use of a high dose of vitamin D (≥800 IU) per day. The inclusion of institutional patients by Chapuy *et al*[38] in the meta-analysis could have affected the finding of the meta-

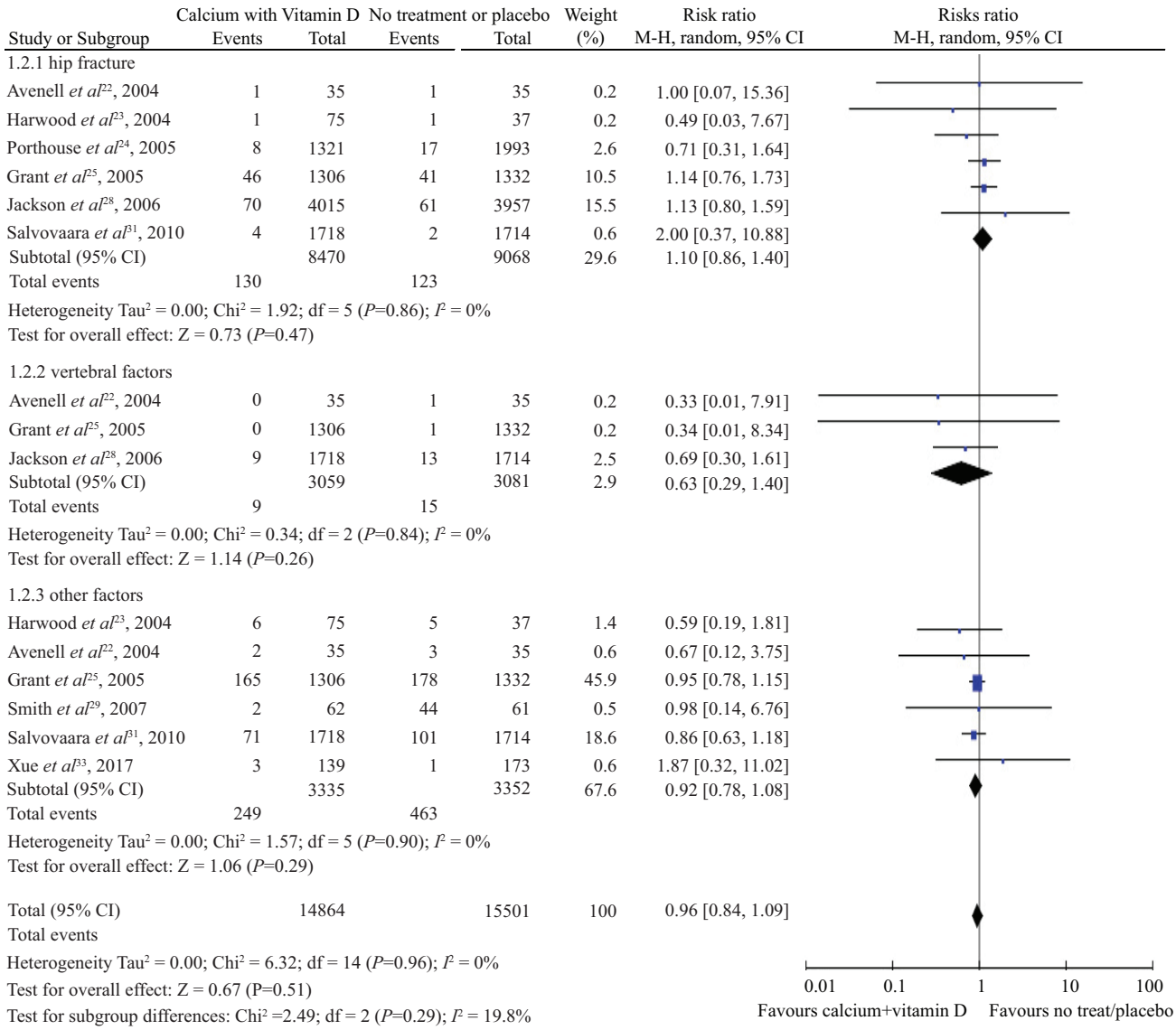

Fig. 4. Forrest plot of trials with the combined administration of calcium and vitamin D for prevention of fracture in hip, vertebrae and other parts of the body.

analysis. Other meta-analyses by Bergman *et al*[39] supported the use of a high dose of vitamin D to prevent the non-vertebral and non-hip fragility fractures. However, they reported no significant association between high dose vitamin D and hip fractures. In the present study, the reason for the difference in the result could be due to reporting of neutral or negative association between vitamin D administration and risk of fracture.

In a Cochrane review by Avenell *et al*[40], the chance of hip fracture or combined fragility fracture was suggestively reduced with the combined administration of calcium and vitamin D. In contrast, Bolland *et al*[41] reported no beneficial effect with the administration of calcium and vitamin D in combination in osteoporotic fractures. A meta-analysis by Zhao *et al*[14] reported inconsistent results with a combined supplementation of calcium and vitamin D due to different inclusion criteria like the restriction of RCTs to community dwellers or residents of nursing homes.

In a study by Jackson *et al*[42], positive interaction was reported between hormonal therapy and calcium and vitamin D supplementation. They concluded that a lower risk of fragility fractures with this combination was found in individuals on hormonal therapy in contrast to the study group not on

Table IV. Subgroup analysis with combined calcium and vitamin D administration for fracture risk prevention

Factor	Participants with fracture	Total number of participants	RR (95% CI)	*P*
Hip fracture				
Combined calcium and vitamin D supplementation				
Calcium with >1 g with low daily vitamin D	120	9454	1.07 (0.75-1.54)	0.83
Other	133	8084	1.12 (0.80-1.57)	
Sex				
Women only	164	14,830	1.07 (0.79-1.46)	0.81
Both sex	89	2708	1.14 (0.76-1.72)	
Serum 25(OH)D levels at presentation				
>20 ng/ml	0	0	NA	NA
<20 ng/ml	251	17,468	1.10 (0.86-1.4)	
Vertebral fracture				
Combined calcium and vitamin D supplementation				
Calcium with >1 g with low daily vitamin D	2	2708	0.34 (0.04-3.2)	0.67
Other	22	3432	0.69 (0.30-1.61)	
Sex				
Women only	22	3432	0.69 (0.30-1.61)	0.45
Both sex	2	2708	0.34 (0.04-3.2)	
Serum 25(OH)D levels at presentation				
>20 ng/ml	0	0	NA	NA
<20 ng/ml	24	6140	0.63 (0.29-1.4)	
Other fracture				
Combined calcium and vitamin D supplementation				
Calcium with >1 g with low daily vitamin D	512	6252	0.91 (0.77-1.07)	0.53
Other	4	123	0.98 (0.14-6.76)	
Sex				
Women only	15	235	0.67 (0.26-1.77)	0.51
Both sex	501	14,988	0.92 (0.78-1.08)	
Serum 25(OH)D levels at presentation				
>20 ng/ml	0	0	NA	NA
<20 ng/ml	516	6375	0.91 (0.77-1.07)	

CI, confidence interval; NA, not available; RR, relative risk

hormonal therapy which did not report any reduction in fracture risk. In the present meta-analysis, all the cases on hormonal therapy were excluded from the analysis.

The data from VITAL trial[43] reported that vitamin D3 supplementation did not reduced risk of fractures.

There is a requirement of a large RCTs, especially in elderly high risk individuals involving combined administration of calcium and vitamin D to obtain a reliable evidence.

The present study did have a few limitations. First, some studies did not include the baseline values of 25(OH)D levels which could have altered the results of the subgroup analysis. Second, few RCTs were of poor quality with allocation bias. Third, there are chances of publication bias in the results reported by individual RCTs. Fourth, there could have been variations in the classification of quality of the studies.

Overall, the present meta-analysis involving RCTs that included calcium and, vitamin D administered

individually or in combination compared with either no treatment or placebo do not support their routine supplementation in the elderly population. However, the results of undergoing RCTs involving high doses of vitamin D may have bearing on the future meta-analyses.

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***Conflicts of Interest*:** None.

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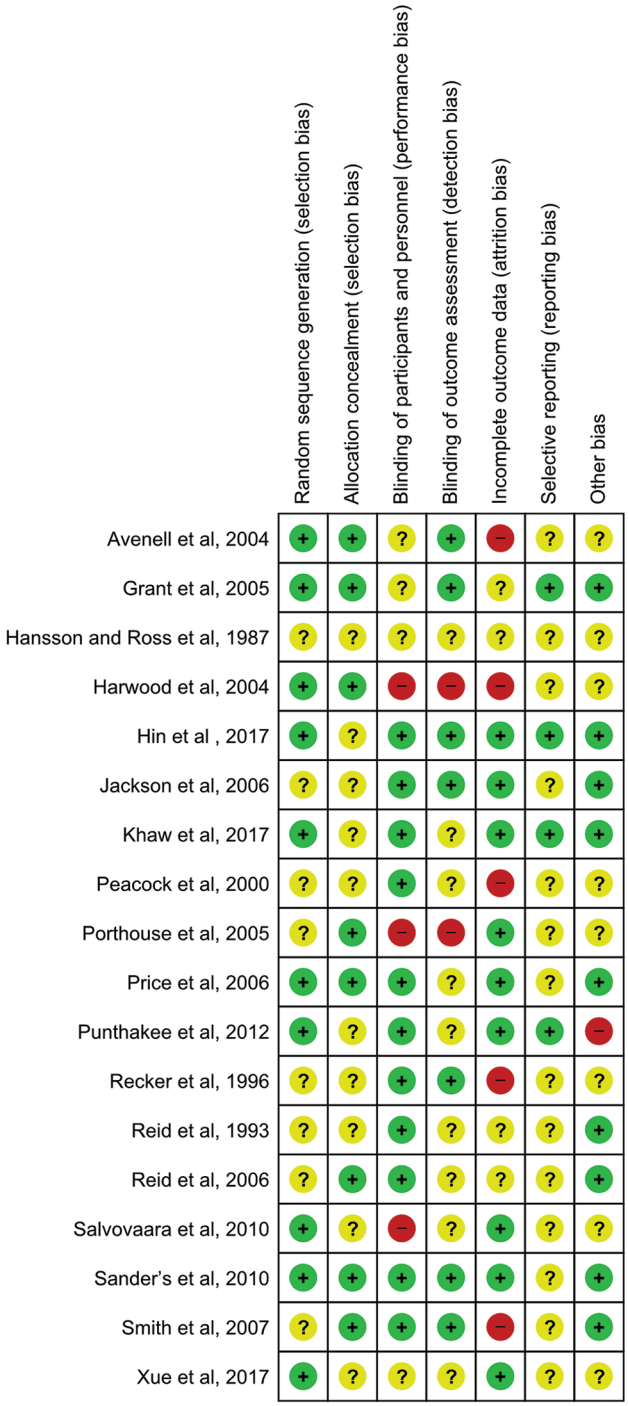
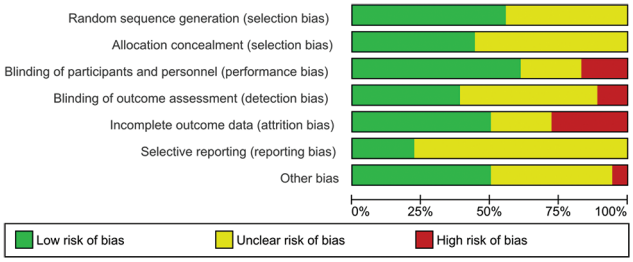
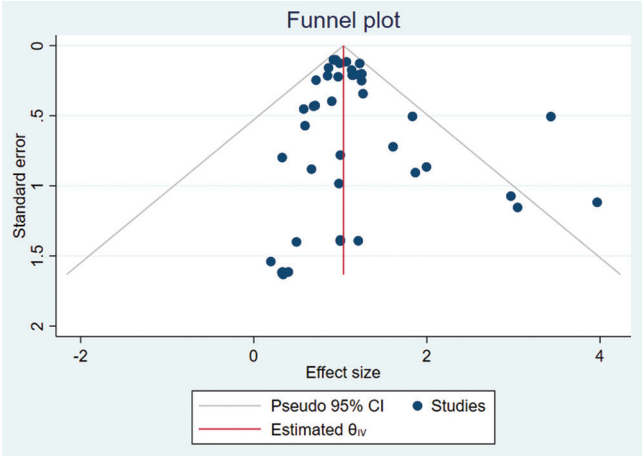


Supplementary Fig. 1. Risk of bias table for included trials.



Supplementary Fig. 2. Risk of bias summary for included trials.



Supplementary Fig. 3. Funnel plot for publication Bias assessment.

Supplementary Material

Search strategy in database

PUBMED:

#1 “calcium”[MeSH Terms] OR “calcium”[All Fields]

#2 “vitamin d”[MeSH Terms] OR “vitamin d”[All Fields] OR “ergocalciferols”[MeSH Terms] OR “ergocalciferols”[All Fields]

#3 “fractures, bone”[MeSH Terms] OR (“fractures”[All Fields] AND “bone”[All Fields]) OR “bone fractures”[All Fields] OR “fracture”[All Fields]

#4 trial”[Title/Abstract] OR “randomised trial”[Title/Abstract] OR “randomised controlled trial” [Title/Abstract]

#5 #1 or #2

#6 #3 and #5

#7 #4 and #6

EMBASE:

#1 ‘calcium’/exp OR calcium

#2 ‘vitamin d’/exp OR ‘vitamin d’

#3 ‘fracture’/exp OR fracture

#4 [cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim

#5 #1 or #2

#6 #3 and 5

#7 #4 and #6

COCHRANE:

#1 calcium:ti,ab,kw

#2 vitamin d:ti,ab,kw

#3 fracture:ti,ab,kw

#4 #1 or #2

#5 #3 and #4

Supplementary Table: List of excluded trials and reasons for the same

Trail excluded	Year of publication	Reason for exclusion
Inkovaara *et al*[1]	1983	Fracture data not reported
Lips *et al*[2]	1996	Fracture data not reported
Dawson-Hughes *et al*[3]	1997	Fracture data not reported
Riggs *et al*[4]	1998	Fracture data not reported
Ruml *et al*[5]	1998	Fracture data not reported
Baron *et al*[6]	1999	Fracture data not reported
Trivedi *et al*[7]	2003	Fracture data not reported
Pfeifer *et al*[8]	2009	Trial did not include no treatment or placebo group
Bischoff-Ferrari *et al*[9]	2010	Trial did not include no treatment or placebo group
Witham *et al*[10]	2010	Trial did not include no treatment or placebo group
Mitri *et al*[11]	2011	Fracture data not reported
Sambrook *et al*[12]	2012	Trial included mandatory sunlight exposure in one of the groups
Schaller *et al*[13]	2012	Fracture data not reported
Rossini *et al*[14]	2012	Trial is non-randomized
Gendenneing *et al*[15]	2012	Fracture data not reported
Aloia *et al*[16]	2013	Fracture data not reported
Witham *et al*[17]	2013	Fracture data not reported
Tella *et al*[18]	2014	Placebo group not included
Takano *et al*[19]	2014	Placebo or no treatment group not included
REVITAHIP trail *et al*[20]	2014	Placebo or no treatment group not included
Massart *et al*[21]	2014	Fracture data not reported
Martineau *et al*[22]	2015	Fracture data not reported
Wang *et al*[23]	2015	Multivitamin tablets were administered in the experimental group
Rolighed *et al*[24]	2015	Fracture data not reported
Uusi-Rasi *et al*[25]	2015	Fracture data not reported
Liu *et al*[26]	2015	Fracture data not reported
Schwetz *et al*[27]	2017	Fracture data not reported
Laiz *et al*[28]	2017	Exercise was included in the intervention group
Pop *et al*[29]	2017	Placebo or no treatment group not included
Leblanc *et al*[30]	2018	Ongoing trial
Joseph *et al*[31]	2018	Ongoing trial
DO-HEALTH[32]	2019	Ongoing trial

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