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SYSTEMATIC REVIEW

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Efficacy and safety of sequential therapy for primary osteoporosis with bone formation promoters followed by bone resorption inhibitors: a meta-analysis

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Abstract

Objective Through this study we aimed to present the latest and most comprehensive pooled analysis, providing an updated evaluation of the efficacy and safety of sequential therapy for primary osteoporosis, using bone formation promoters followed by bone resorption inhibitors.

Methods PubMed, the Cochrane Library, Web of Science, and Embase databases were retrieved to identify pertinent studies. Randomized controlled trials (RCTs) on the sequential therapy of primary osteoporosis with bone formation promoters followed by bone resorption inhibitors were included. Data from clinical studies that met the eligibility criteria were extracted, and quality assessment and meta-analysis were performed using RevMan v5.4 and Stata v15.0. Sensitivity and subgroup analyses were performed to find the source of heterogeneity and discover more findings.

Results A total of 10 eligible articles involving 14,510 patients (7171 in the intervention group versus 7339 in the comparator group) were included for the evidence synthesis. The baseline characteristics of the two groups were similar. Pooled analysis showed that the intervention group (bone formation promoters followed by bone resorption inhibitors) increased BMD at the spine (SMD:1.64; 95% CI: 0.97, 2.31; $P < 0.00001$; $I^2 = 99\%$), femoral neck (SMD: 0.57; 95% CI: 0.16, 0.99; $P = 0.007$; $I^2 = 96\%$), and total hip (SMD: 0.82; 95% CI: 0.16, 1.48; $P = 0.02$; $I^2 = 97\%$) compared with the comparator group (monotherapy or combination therapy using two drugs)for postmenopausal osteoporosis patient; however, there was no statistically significant difference observed in the increase of BMD at the 1/3 distal radius comparing the intervention group and comparator group (SMD: -0.25; 95% CI: -1.49, 0.99; $P = 0.069$; $I^2 = 92\%$). The incidence of new fractures was reduced in the intervention group relative to the comparator group (RR: 0.60; 95% CI: 0.43, 0.82; $P = 0.001$; $I^2 = 75\%$). The incidence of adverse events differed statistically between the two groups (RR: 0.85; 95% CI: 0.76, 0.95; $P = 0.004$; $I^2 = 97\%$), but the difference in adverse event incidence was not statistically significant among subgroups within the intervention and comparator groups. The intervention group had a superiority of Clinical efficacy.

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Conclusion Among patients with primary osteoporosis, sequential therapy with bone formation promoters followed by bone resorption inhibitors substantially increased BMD at sites such as the spine, femoral neck, and total hip while concurrently mitigating fracture risks. However, benefits regarding BMD at the 1/3 distal radius and the incidence of adverse events have not yet been established.

Study registration Registered on PROSPERO (ID: CRD42023437188).

Keywords Primary osteoporosis, Sequential therapy, Meta-analysis

Introduction

As the world's population ages, the prevalence of osteoporosis is increasing. Osteoporotic fracture is a potentially serious consequence of osteoporosis, which is a major cause of disability and even death in elderly patients [1–10]. Osteoporosis and related fractures have become a major global public health challenge. However, awareness, diagnosis, and treatment rates of osteoporosis are quite low [11–13]. Currently, the primary clinical treatment for osteoporosis involves pharmacotherapy. Effective pharmacotherapy could increase bone mineral density (BMD) and lower fracture risks. Therapeutic drugs for osteoporosis encompass various types, primarily bone resorption inhibitors, bone formation promoters, dual-action drugs, and other mechanism-specific medications. These medications exert different mechanisms of action during the treatment of osteoporosis. Despite significant progress in the prevention and management of osteoporosis with various anti-osteoporosis drugs, the selection of osteoporosis drugs and therapy strategies, including combination therapy and sequential therapy, are still under exploration.

Sequential therapy for primary osteoporosis represents a strategic and staged methodology for managing the condition, involving the administration of diverse medications with distinct mechanisms of action at various phases of the treatment regimen. This approach is designed to optimize therapeutic outcomes by targeting both bone formation and bone resorption processes at the most opportune times [14]. Indications for sequential drug therapy include: (i) Failure of bone resorption inhibitor therapy, extended therapy duration, or adverse reactions; (ii) Recommended course of therapy is due (e.g., Teriparatide), but the patient still has a high fracture risk requiring continued therapy; (iii) Maintenance of therapy effects is required after discontinuation of short-acting drugs such as Teriparatide or Denosumab [15–17]. Main regimens for sequential therapy of primary osteoporosis based on drug action mechanisms are: (i) Bone formation promoters followed by bone resorption inhibitors; (ii) Bone resorption inhibitors followed by bone formation promoters; (iii) Different types of bone resorption inhibitors in sequence. Among these, the sequential therapy of primary osteoporosis with bone formation promoters followed by bone resorption inhibitors is a recommended approach in clinical trials [18].

Currently, there exists no definitive consensus on the precise strategy for the sequential therapy of primary osteoporosis with bone formation promoters followed by bone resorption inhibitors. Therefore, the purpose of this study was to conduct a systematic review and meta-analysis of data from clinical studies to obtain higher-quality and more comprehensive clinical evidence concerning the safety and efficacy of the therapy in treating primary osteoporosis.

Materials and methods

Retrieval strategy

Relevant literature was retrieved through searches conducted in PubMed, the Cochrane Library, Web of Science, and Embase, with the time span covering all records from the database inception up to December 31, 2023. MeSH plus free-text words were adopted for the search. MeSH included "Anabolic drugs, Teriparatide, Abaloparatide, Parathyroid hormone, Romosozumab, Antiresorptive drugs, Bisphosphonates, Denosumab, Raloxifene"; free-text words adopted included terms to relevant the MeSH listed in the MeSH vocabulary. The detailed search strategy is presented in Supplementary Table (S1). This systematic review adhered to the guidelines outlined in the PRISMA statement and was registered on PROSPERO (ID: CRD42023437188).

Eligibility criteria in this study

Criteria for inclusion

(i) All randomized controlled trials (RCTs) published in English by December 31, 2023, in the searched databases. (ii) The study population consisted of patients with primary osteoporosis (Bone mineral density was measured by dual-energy X-ray absorptiometry (DXA) with a T score lower than average bone mineral density in healthy young adults of the same sex and race − 2.5 standard deviations (SD) or when fragility fractures were present.) (iii) The intervention group received bone formation promoters followed by bone resorption inhibitors; the comparator group received monotherapy or the combination of two drugs (specific varieties, administration, and dosage of the various drugs were not restricted). (iv) Outcome measures encompassed changes in BMD,

respectively at the spine, femoral neck, total hip, and the 1/3 distal radius from baseline (both in percentage and absolute values), as well as fracture risk, and incidence of adverse events.

Exclusion criteria

(i) Reviews, meta-analyses, comments and responses, basic experimental studies, and case reports. (ii) Observational studies, experimental studies that were not RCTs. (iii) Studies where the study population and intervention did not conform to the criteria for inclusion. (iv) Studies where data on outcome measures were unavailable.

Literature screening process and the extraction of data

Two authors (Yuxin Liu, Xin Liu) of the study independently screened the literature and extracted the data. Any discrepancies were resolved by reaching a consensus with the assistance of a third researcher (Tao Luo). Irrelevant publications were removed by screening the studies' titles and abstracts. Subsequently, full texts of the remaining articles were thoroughly read to identify studies aligning with the defined inclusion criteria. The two researchers independently extracted data including the region of the study, registration ID, basic information on study design, baseline data of subjects, and outcome measures, with results cross-checked for accuracy. When data were missing or not reported in the study, we contacted the corresponding authors to obtain complete data if available. When discrepancies were found during the data extraction process, two authors re-examined the original data sources to ensure the accuracy of the information. This process included cross-checking multiple sources when available to confirm the correct data points. In cases where discrepancies were unclear or complex, we consulted with a third researcher, to reach a consensus on the most accurate data interpretation.

Risk of bias assessment of studies included

For the risk of bias assessment of studies, the tool for RCTs, as recommended by the Cochrane Handbook 5.1.0 was adopted. Studies were evaluated for quality across seven domains: random sequence generation, allocation concealment, the blinding of participants and personnel, the blinding of outcome assessment, completeness of outcome data, selective reporting, and other bias sources. For each domain, the risk was categorized into low, high, or unclear. Studies with a low risk of bias were considered to provide higher levels of evidence. Two researchers independently performed the bias risk assessment and cross-checked the results.

Statistical methods

Evidence synthesis was performed using Review Manager v5.4. Data in different units were pooled using standard mean differences (SMDs). The SMD and relative risk (RR) were applied for the comparison of continuous and dichotomous variables, respectively. All metrics were reported with a 95% CI. Heterogeneity in studies was assessed through the chi-squared ($\chi 2$) test (Cochran's Q) and inconsistency index (I^2). $\chi 2$ p value < 0.05 or $I^2 > 50\%$ was considered as significant heterogeneity. A random-effects model was used to estimate the combined SMD or RR when significant heterogeneity was detected ($\chi 2$ p value < 0.05 or $I^2 > 50\%$). Otherwise, the fixed-effect model was applied. In addition, we performed one-way sensitivity analyses to evaluate the effect of included studies on the combined results for outcomes with significant heterogeneity. Publication bias was evaluated visually by creating funnel plots *via* Review Manager v5.4, as well as by conducting Egger's regression tests using the Stata v15.0 for outcomes with 10 included studies. p value < 0.05 was considered as Subgroup analysis was performed according to various regimens, therapy durations, and experimental regions.

Results

Results of literature screening

After developing search strategies based on the study topic, a total of 6966 related publications were retrieved from the databases up to December 31, 2023. Through preliminary screening after title or abstract review, non-English studies, studies not related to the subject of our study, review and meta-analysis, responses and comments, basic experiments, and case reports were excluded. Upon further scrutiny of the methodology and data analysis of the remaining 34 studies, non-RCTs and studies with irrelevant interventions and controls or without extractable data were excluded. Ultimately, 10 studies [18–27] were included in the analysis (Fig. 1).

Basic study characteristics

The subjects in the 10 included studies were postmenopausal women, the trial regions were from Europe, the Americas and Asia, and all studies were RCTs. The interventions included in the study were various regimens of bone formation promoters followed by bone resorption inhibitors: (i) Parathyroid hormone followed by Alendronate; (ii) Teriparatide followed by Alendronate; (iii) Teriparatide followed by Denosumab; (iv) Teriparatide followed by Raloxifene; (v) Abaloparatide followed by Alendronate; (vi) Romosozumab followed by Alendronate; (vii) Romosozumab followed by Denosumab. The duration of therapy ranged from 24 to 48 months. The study design and baseline characteristics of the study population of the 10 included studies are provided in

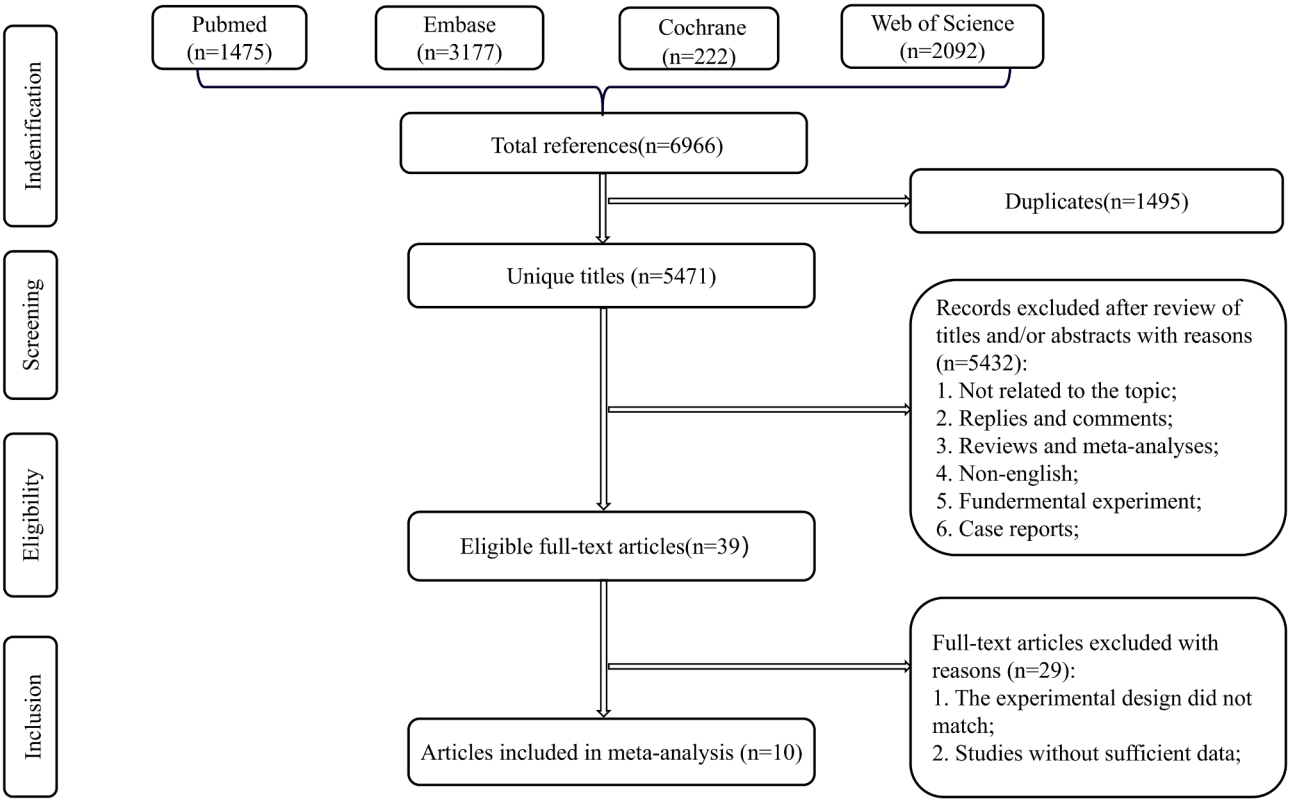

Fig. 1 Flowchart of the systematic search and selection process

Table 1. No statistically significant differences in age and body mass index (BMI) were found between the intervention and comparator groups, allowing for comparative analysis, as shown in Fig. 2.

Methodological quality assessment of the studies included

As per the Cochrane Handbook (v5.1.0), the studies included were evaluated for quality across seven domains, encompassing random sequence generation, allocation concealment, the blinding of participants and personnel, the blinding of outcome assessment, completeness of outcome data, selective reporting, and other bias sources. All (10) studies employed randomized allocation methods, with no selective bias or other sources of bias, indicating low risk in these aspects; the use of blinding in assessing outcome measures was of moderate risk; risks associated with allocation concealment, patient and experimenter blinding, and outcome data integrity are relatively high, which may be due to the study's reliance on long-term drug therapy studies, where open-label and loss to follow-up rates were unavoidable. The quality assessment of these studies is described in Fig. 3: The risk of bias graph is shown in Fig. 3a, and the risk of bias summary is shown in Fig. 3b.

Meta-analysis results

BMD

Spine BMD Data on changes in Spine BMD were synthesized from 8 studies, including 6196 patients (3078 in the intervention group versus 3118 in the comparator group). Pooled analysis revealed significantly higher changes of the spine BMD in the intervention group (SMD: 1.64; 95% CI: 0.97, 2.31; $P < 0.00001$) with a significant heterogeneity ($I^2 = 99\%$, $P < 0.00001$)(Fig. 4a). The funnel plot (Fig. 5) and Egger's test ($P = 0.224$) revealed no publication bias.

Femoral neck BMD Analysis of changes in femoral neck BMD was conducted in 7 studies with 5919 patients (2943 in the intervention group versus 2976 in the comparator group). Pooled analysis detected significantly higher changes of the femoral neck BMD in the intervention group (SMD: 0.57; 95% CI: 0.16, 0.99; $P = 0.007$) with a significant heterogeneity ($I^2 = 96\%$, $P < 0.00001$) (Fig. 4b). The funnel plot (Fig. 5) and Egger's test ($P = 0.578$) revealed no publication bias.

Total hip BMD Five studies involving 5503 patients (2740 in the intervention group versus 2763 in the comparator group) were included in the analysis. Pooled analysis revealed significantly higher changes in the total hip BMD in the intervention group (SMD: 0.82; 95% CI: 0.16,

Table 1 Basic characteristics of the included studies

Study	Country	Registration number	Study design	Population	Duration of therapy(month)	Patients (*n*)	Age(year)		Body mass index(kg/m²)		Intervention		Endpoint
						Intervention group/Comparator group	Intervention group/Comparator group		Intervention group/Comparator group		Intervention group/Comparator group		
Rittmaster2000	Canada	/	prospective	Postmenopausal women	24	18/19	64 ± 5	64 ± 5	32 ± 8	32 ± 8	Parathyroid Hormone→Alendronate	Placebo→Alendronate	①②
Black 2005 a	USA	/	prospective	Postmenopausal women	24	59/60	68.7 ± 7.4	70.1 ± 7.3	25.4 ± 4.9	25.9 ± 4.3	Parathyroid Hormone→Alendronate	Parathyroid Hormone→Placebo	①②④
b	USA	/	prospective	Postmenopausal women	24	59/59	68.7 ± 7.4	70.2 ± 6.8	25.4 ± 4.9	27.1 ± 5.6	Parathyroid Hormone→Alendronate	Parathyroid Hormone combined Alendronate→Alendronate	①
c	USA	/	prospective	Postmenopausal women	24	59/60	68.7 ± 7.4	70.7 ± 6.8	25.4 ± 4.9	25.1 ± 4.5	Parathyroid Hormone→Alendronate	Alendronate→Alendronate	①
Hagino2021	JAN	jRCTs031180235 UMIN000015573	prospective	Postmenopausal women	30	489/496	49.6 ± 4.4	49.2 ± 4.4	22.2 ± 3.8	22.1 ± 3.5	Teriparatide→Alendronate	Alendronate→Alendronate	⑤⑥
Leder2015	USA	NCT00926380	prospective	Postmenopausal women	48	27/23	66.1 ± 7.9	65.3 ± 8	25.5 ± 3.7	25.9 ± 5.2	Teriparatide→Denosumab	Teriparatide combined denosumab →denosumab	①②③④
Adami2007	Italy	/	prospective	Postmenopausal women	24	157/172	66.1 ± 7.9	65.3 ± 8	/	/	Teriparatide→Raloxifene	Teriparatide→Placebo	①②
Eastell2009	UK	/	prospective	Postmenopausal women	24	97/102	69.4 ± 7	69.1 ± 8.6	/	/	Teriparatide→Raloxifene	Teriparatide→no active therapy	①②③⑤⑥
Bone2018	USA	/	prospective	Postmenopausal women	43	558/581	70.2 ± 6.54	70.1 ± 6.29	24.9 ± 3.67	25 ± 3.62	Abaloparatide→Alendronate	Placebo→Alendronate	①②③⑤⑥
Saag2017	USA	NCT01631214	prospective	Postmenopausal women	36	2046/2047	74.4 ± 7.5	74.2 ± 7.5	25.46 ± 4.41	25.36 ± 4.42	Romosozumab→Alendronate	Alendronate→Alendronate	①②③⑤⑥
McClung2018	USA	NCT00896532	prospective	Postmenopausal women	36	129/131	66.8 ± 6.5	66.2 ± 6.5	25.4 ± 4.9	25.4 ± 4.9	Romosozumab→Alendronate	Alendronate→Alendronate	①③
Lewiecki2019	USA	NCT01575834	prospective	Postmenopausal women	36	3591/3589	70.6 ± 6.9	70.5 ± 6.8	24.7 ± 4.3	24.7 ± 4.4	Romosozumab→Denosumab	Placebo→Denosumab	⑤⑥

①Changes in bone mineral density at the spine

②Changes in bone mineral density at the femoral neck

③Changes in bone mineral density at the total hip

④Changes in bone mineral density at the 1/3 distal radius

⑤Fracture risk

⑥Incidence of adverse events

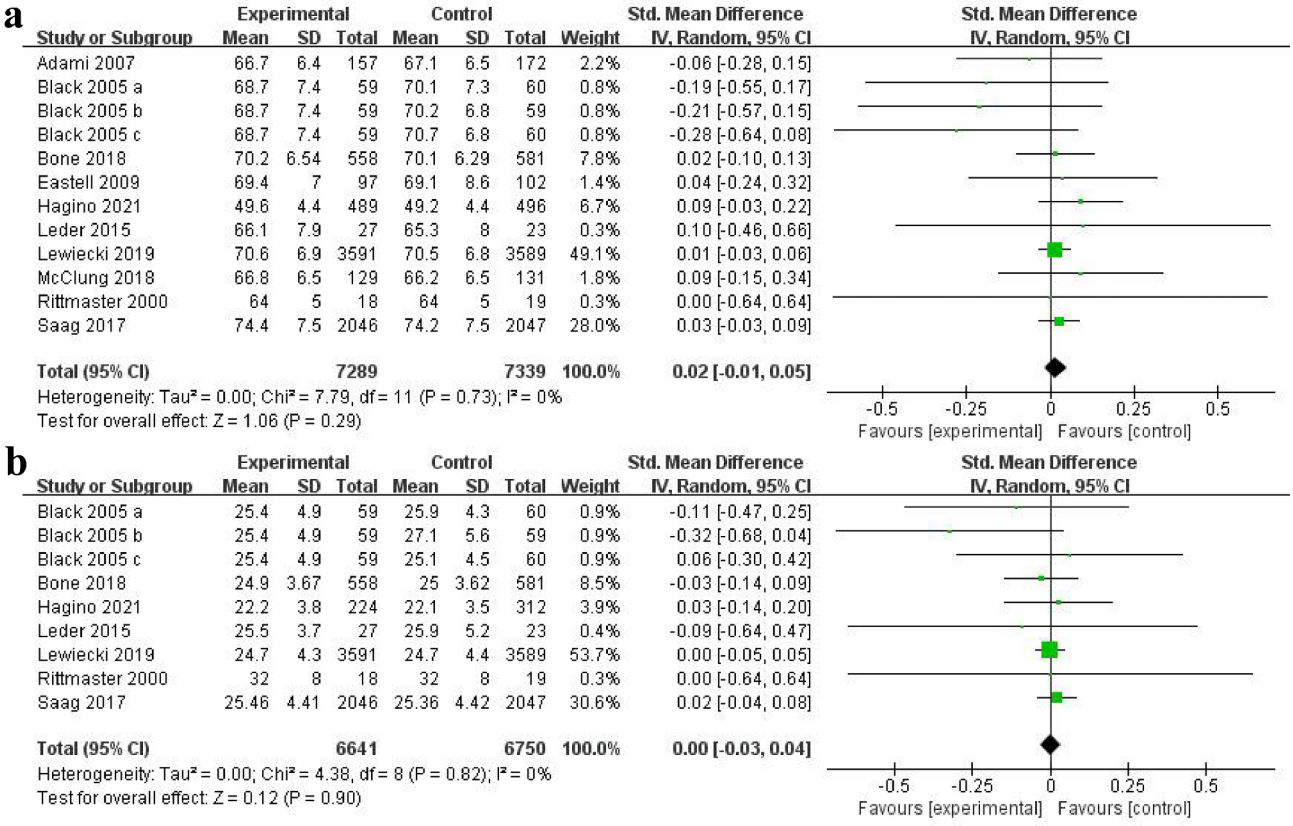

Fig. 2 Meta-analysis of age and body mass index of the included studies population

1.48; $P = 0.002$) with a significant heterogeneity ($I^2 = 97\%$, $P < 0.00001$) (Fig. 4c). The funnel plot (Fig. 5) and Egger's test ($P = 0.701$) indicated no publication bias.

BMD at the 1/3 distal radius Two articles reported the data of BMD at the 1/3 distal radius, including 169 patients (86 in the intervention group versus 83 in the comparator group). Pooled results demonstrated that the changes in BMD at the 1/3 distal radius were similar between the two groups (SMD: -0.25; 95% CI: -1.49, 0.99; $P = 0.069$) with a significant heterogeneity ($I^2 = 92\%$, $P < 0.0003$) (Fig. 4d). The funnel plot (Fig. 5) and Egger's test ($P = 0.242$) revealed no publication bias.

Fracture risk

Data on the fracture risk were available in 5 studies with 14,163 patients (6961 in the intervention group versus 7202 in the comparator group). Evidence synthesis showed that the intervention group had lower fracture risk (RR: 0.60; 95% CI: 0.43, 0.82; $P = 0.001$) (Fig. 4e) with a significant heterogeneity ($I^2 = 75\%$, $P = 0.003$). The funnel plot (Fig. 5) and Egger's test ($P = 0.708$) revealed no publication bias.

Incidence of adverse events

Five studies with 13,219 patients (6541 in the intervention group versus 6678 in the comparator group) were included in the analysis for incidence of adverse events. Pooled analysis indicated that the intervention group had a lower incidence of adverse events (RR: 0.85; 95% CI: 0.76, 0.95; $P = 0.004$) with a significant heterogeneity($I^2 = 97\%$, $P < 0.00001$)(Fig. 4f). The funnel plot (Fig. 5) and Egger's test result ($P = 0.282$) revealed no publication bias.

Sensitivity analysis

We conducted one-way sensitivity analyses to compare changes in spinal BMD, femoral neck BMD, total hip BMD, fracture risk, and the incidence of adverse events to evaluate the influence of each study on the combined outcomes by removing the individual study one. The sensitivity analysis revealed that the new combined outcomes remained constant after the exclusion of any individual study for the spine BMD (Fig. 6a) and fracture risk(Fig. 6d). However, when we excluded the data reported by Eastell et al. [24] or Saag et al. [26], the statistical results in femoral neck BMD between the two groups have changed (Fig. 6b). Analogously, changes in the statistical results for total hip BMD were observed when the data reported by Bone et al. [25], Eastell et

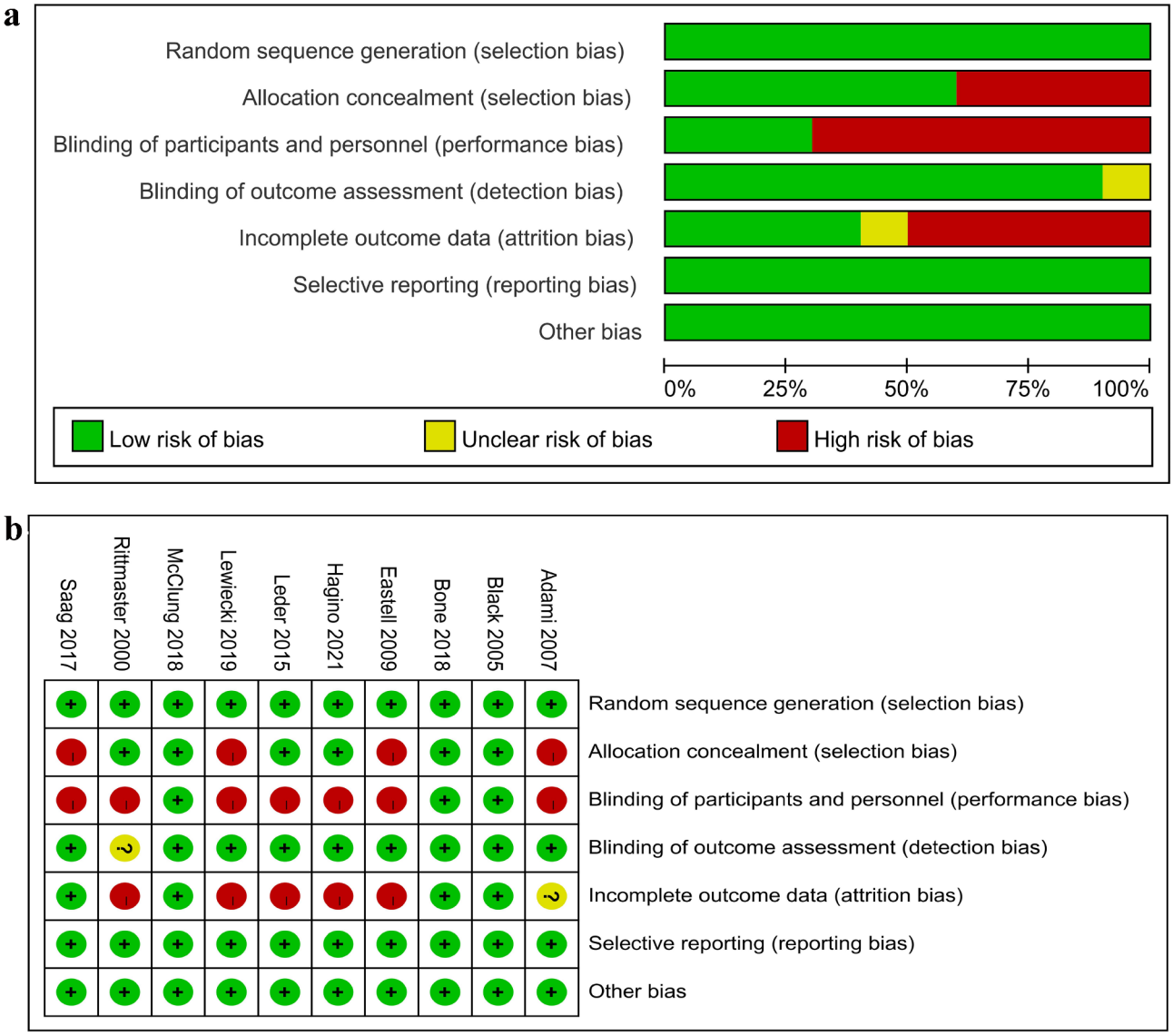

Fig. 3 Quality assessment of the included studies

al. [24], McClung et al. [19], and Saag et al. [26] were excluded one by one (Fig. 6c). Additionally, excluding the data reported by Hagino et al. [22] led to changes in the statistical results for the incidence of adverse events (Fig. 6e). Statistical changes obtained may be related to differences in study design, intervention duration, intervention measures, and sample sizes, as shown in Fig. 6.

Subgroup analysis

Subgroup analysis was performed on the 10 included studies, which were divided into different subgroups according to therapy time, different experimental areas, and various regimens. Five outcome indicators including spine BMD, femoral neck BMD, total hip BMD, distal third of radius BMD, fracture risk, and adverse events were analyzed. The research areas cover Asia, Europe, and the Americas, and the therapy time covers groups greater than or equal to 36 months and less than 36 months. The various regimens cover the Parathyroid hormone followed by the bone resorption inhibitors subgroup, Teriparatide/Abaloparatide followed by the bone resorption inhibitors subgroup, and Romosozumab followed by the bone resorption inhibitors subgroup.

Statistically differences in changes of spine BMD were observed across the American subgroup, various therapy duration subgroups, the parathyroid hormone followed by bone resorption inhibitors subgroup, and the teriparatide/abaloparatide followed by bone resorption inhibitors subgroup. Notably, heterogeneity decreased in the parathyroid hormone followed by the bone resorption inhibitors subgroup, while it remained consistent with the overall population in the other subgroups. Variations

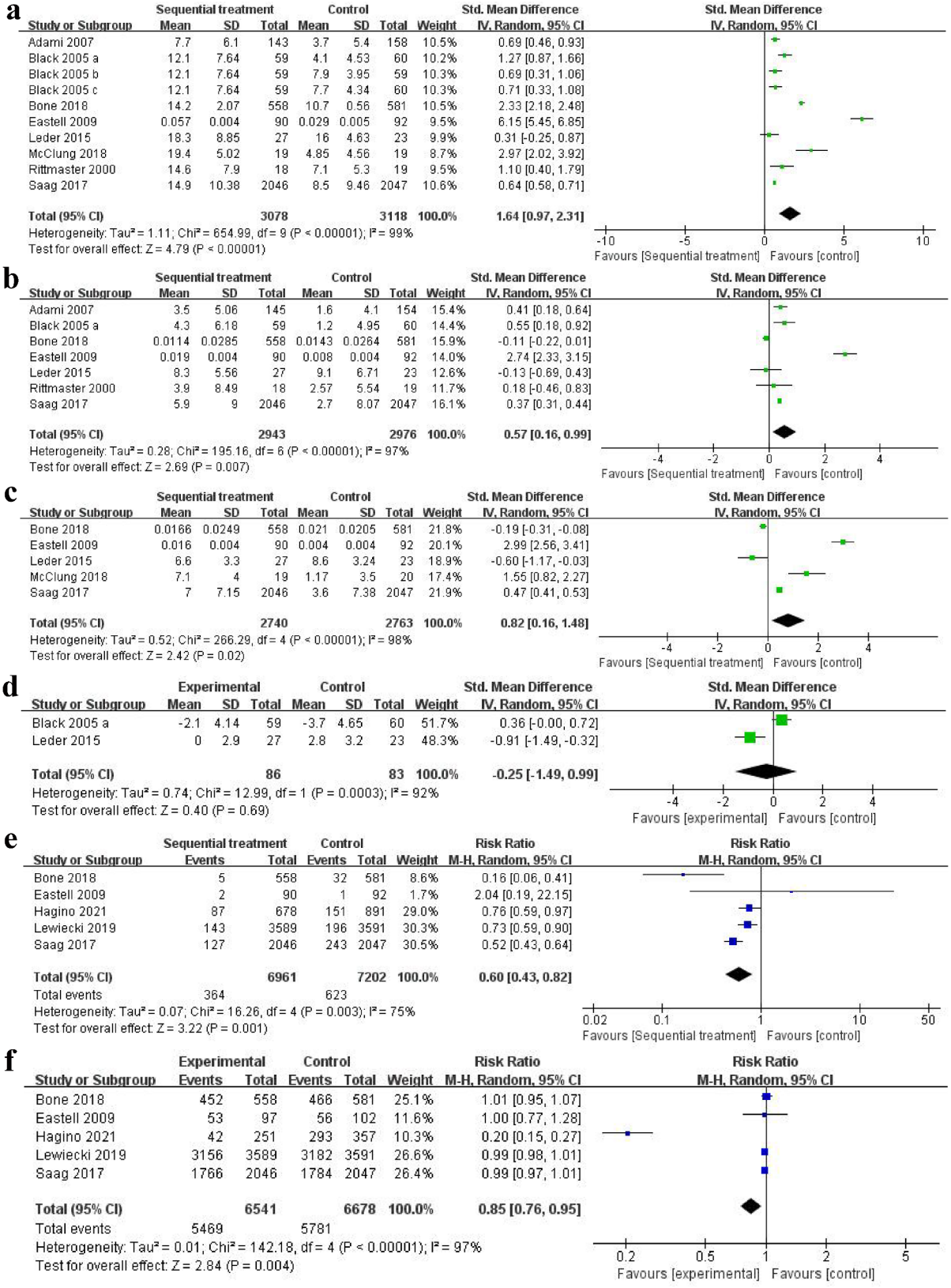

Fig. 4 Meta-analysis of bone mineral density change of spine, bone mineral density change of femoral neck, bone mineral density change of total hip, bone mineral density change of 1/3 distal radius, fracture risk, and incidence of adverse events

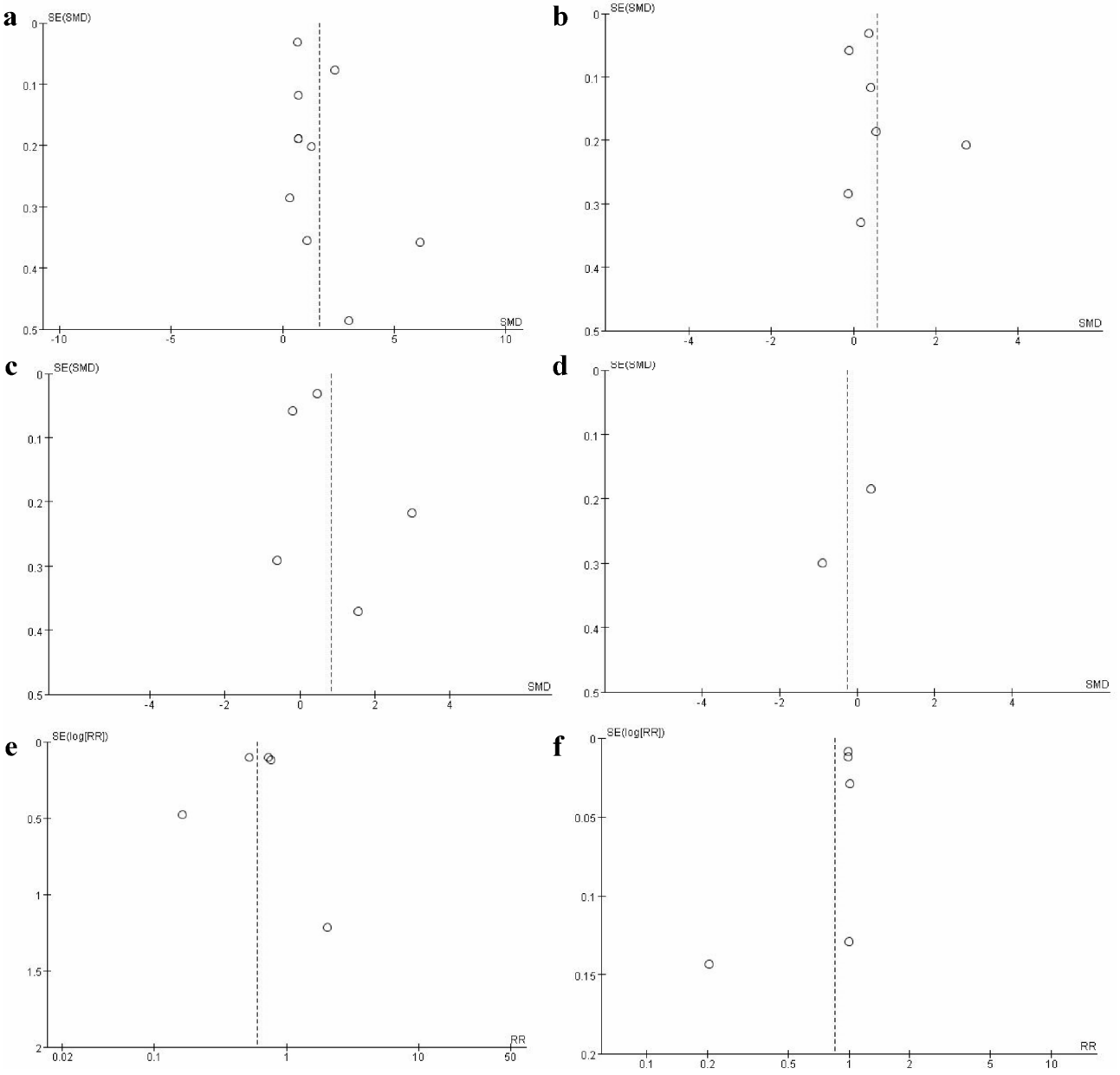

Fig. 5 Funnel plot of bone mineral density change of spine, bone mineral density change of femoral neck, bone mineral density change of total hip, bone mineral density change of 1/3 distal radius, fracture risk, and incidence of adverse events

in changes of femoral neck BMD were found in the Parathyroid hormone followed by the bone resorption inhibitors subgroup and the romosozumab followed by the bone resorption inhibitors subgroup, with a marked reduction in heterogeneity in the former. Differences in changes in total hip BMD were statistically significant in the European subgroup and the subgroup with a therapy duration of less than 36 months, maintaining consistent heterogeneity with the overall analysis. Regarding fracture risk, differences were statistically significant in the Asian and American subgroups, various therapy duration subgroups, and the romosozumab followed by the bone resorption inhibitors subgroup. Heterogeneity was notably reduced in the subgroup with therapy duration less than 36 months, while it remained consistent with the overall population in the other subgroups. As for adverse events, a statistical difference was observed in the Asian subgroup, based on a single study. No statistical differences in adverse event rates were found in other subgroups, suggesting low reliability of the initial results and insufficient evidence to conclude a difference in adverse event rates between the two groups. The above subgroup analyses are summarized in Table 2.

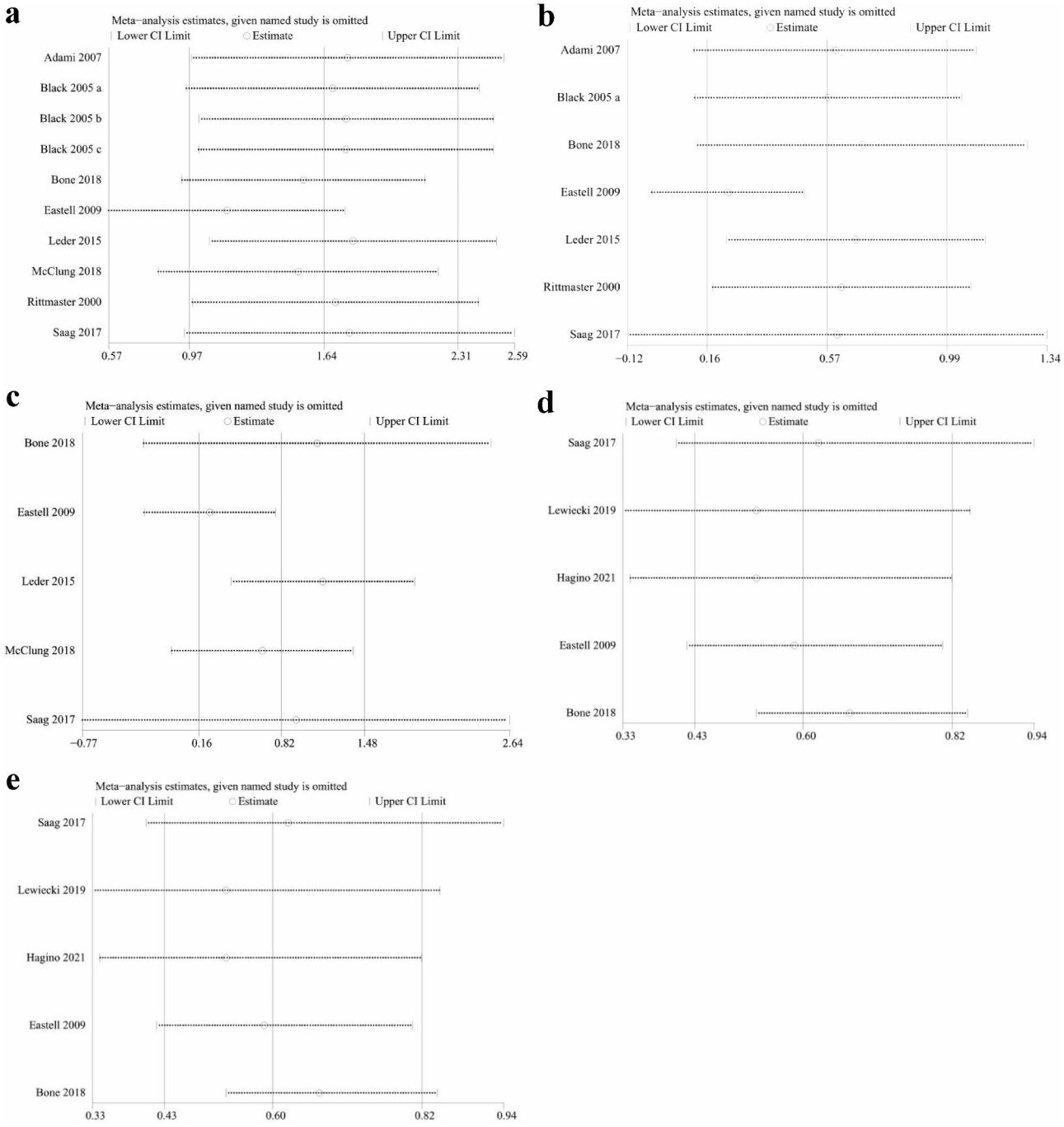

Fig. 6 Sensitivity analysis

Discussion

In the past 30 years, efforts have been continuously made to develop new treatments for osteoporosis. Multiple exploratory studies have been conducted in both basic medical research [28–30] and clinical trials for osteoporosis [31–33]. Now, we have potent interventions that could reduce bone resorption and increase bone formation. Commonly used anti-osteoporosis monotherapy includes Teriparatide, Abaloparatide, Alendronate, Raloxifene, Denosumab, and Romosozumab. The above monotherapies could gain bone mineral density and reduce the risk of fracture in patients with osteoporosis to varying degrees [34–37]. Although significant progress has been made in the prevention and treatment of osteoporosis with various anti-osteoporosis drugs, there is now a notable slowdown in the development of therapeutic agents [38, 39]. Consequently, the research agenda must now shift towards the optimal use of available drugs

Table 2 Subgroup analysis

Subgroup		Changes in bone mineral density at the spine				Changes in bone mineral density at the femoral neck				Changes in bone mineral density at the total hip				Fracture risk				Incidence of adverse events			
		Number of studies	SMD [95%CI]	*P* value	I^2	Number of studies	SMD [95%CI]	*P* value	I^2	Number of studies	SMD [95%CI]	*P* value	I^2	Number of studies	SMD [95%CI]	*P* value	I^2	Number of studies	SMD [95%CI]	*P* value	I^2
Total		10	1.64 [0.97, 2.31]	<0.00001	99%	7	0.57 [0.16, 0.99]	0.007	97%	5	0.82 [0.16, 1.48]	0.02	98%	5	0.60[0.43, 0.82]	0.001	75%	5	0.85[0.76, 0.95]	0.004	97%
Region	Asian	0				0				0				1	0.76[0.59, 0.97]	0.03		1	0.20[0.15, 0.27]	<0.00001	
	Europe	3	2.64[-0.51,5.78]	0.1	99%	3	1.12 [-0.51, 2.74]	0.18	98%	1	2.99 [2.56, 3.41]	<0.00001		1	2.04 [0.19,22.15]	0.56		1	1.00[0.77, 1.28]	0.97	
	America	7	1.24 [0.49, 1.99]	0.001	99%	4	0.19 [-0.16, 0.53]	0.29	95%	4	0.24 [-0.28, 0.77]	0.36	97%	3	0.50[0.32, 0.79]	0.003	84%	3	0.99[0.98, 1.01]	0.29	0%
Duration of therapy(month)	At least 36 months	4	1.53 [0.36, 2.70]	0.01	99%	3	0.08 [-0.33, 0.48]	0.71	96%	4	0.24 [-0.28, 0.77]	0.36	97%	3	0.50[0.32, 0.79]	0.003	84%	3	0.99[0.98, 1.01]	0.29	0%
	Less than 36 months	6	1.73 [0.66, 2.81]	0.002	98%	4	0.98 [-0.12, 2.07]	0.08	97%	1	2.99 [2.56, 3.41]	<0.00001		2	0.77[0.60, 0.98]	0.03	0%	2	0.45[0.08, 2.44]	0.36	99%
Various regimens	Parathyroid hormone→Bone resorption inhibitors	4	0.91 [0.60, 1.21]	<0.00001	50%	2	0.46[0.14, 0.78]	0.005	0%	0				0				2	0.99[0.98, 1.01]	0.29	0%
	Teriparatide/Abaloparatide→Bone resorption inhibitors	4	2.34 [0.83, 3.85]	0.002	99%	4	0.73 [-0.28, 1.74]	0.16	98%	3	0.73[-1.35, 2.81]	0.49	98%	3	0.51[0.14, 1.84]	0.31	81%	0			
	Romosozumab→Bone resorption inhibitors	2	1.76 [-0.52, 4.03]	0.13	96%	1	0.37[0.31, 0.44]	<0.00001		2	0.95[-0.11, 2.00]	0.08	88%	2	0.62[0.45, 0.86]	0.004	80%	3	0.59[0.20, 1.78]	0.35	99%

to treat individuals at risk of fracture, with long-term treatment strategies for osteoporosis drugs and various regimens involving drugs with different mechanisms still being explored.

Certain original clinical trial data demonstrated that sequential therapy yielded benefits to varying degrees compared to monotherapy. Teriparatide followed by Denosumab could effectively increase BMD at various sites in postmenopausal women with severe osteoporosis [40]. Teriparatide followed by bisphosphonates [41, 42] or Denosumab [43, 44] both achieved further increases in BMD, with patients sequentially treated with Denosumab showing greater increases in BMD at sites such as lumbar spine, total hip, and femoral neck than those sequentially treated with oral bisphosphonates. In another study, Teriparatide followed by Denosumab resulted in a larger increase in vertebral BMD than that followed by bisphosphonates [45]. After 2 years of treatment using Teriparatide followed by Raloxifene, vertebral BMD was maintained, but total hip and femoral neck BMD significantly increased [46]. Compared to 2 years of treatment using Romosozumab followed by zoledronic acid, Romosozumab followed by Denosumab demonstrated more substantial increases in BMD, especially in lumbar spine BMD [47]. Compared to 24 months of treatment using alendronate sodium alone, a regimen of 12-month Romosozumab following 12-month alendronate sodium resulted in a reduction of vertebral, non-vertebral, and hip fracture risks by 48%, 20%, and 38%, respectively [25]. For postmenopausal women with osteoporosis, Romosozumab followed by bone resorption inhibitors exhibited larger increases in BMD than bone resorption inhibitor treatment alone [48].

The detailed plan and suitable population for sequential drug therapy are still widely debated worldwide. Under these conditions, we performed a newer and more extensive systematic review and pooled analysis of 10 comparative studies, including 14,510 patients, and our results revealed several findings. First, all included studies were RCTs, which typically provide better control over confounding factors compared to other study designs. The sequential administration of bone formation promoters followed by bone resorption inhibitors demonstrates efficacy in enhancing bone mineral density at the spine, total hip, and femoral neck and reducing fracture risk; however, no significant differences are observed in the 1/3 distal radius. Our findings validate previous studies that have reported the superiority of sequential therapy with bone formation promoters followed by bone resorption inhibitors. This therapeutic approach enhances the efficacy of anti-osteoporosis therapy, which holds significant clinical relevance for patients requiring long-term management of osteoporosis. While the BMD gains at key sites like the femoral neck and total hip may be modest, they hold significant clinical importance: (i) Reducing fracture risk: Femoral neck and total hip are common fracture sites in older adults, the modest BMD gains can enhance bone resistance, reducing fracture risk from falls and supporting articular surfaces; (ii) Improving surgical outcomes: BMD is critical in orthopedic surgeries, especially hip procedures. Adequate BMD ensures implant stability, reduces loosening/failure, and promotes healing; (iii) Enhancing skeletal health: Modest BMD gains can slow the progression of osteoporosis, maintaining skeletal integrity and improving long-term bone health [49]. Secondly, the pooled analysis of all subgroups except 1 trial showed no statistical difference in the incidence of adverse events, so sequential therapy cannot be considered an advantage in reducing the incidence of adverse events. Third, based on the statistical results, subgroup analyses found that sequential treatment was more reliable in increasing spine BMD and reducing fracture risk in the American population. Among the various regimens, the Parathyroid hormone followed by bone absorption inhibitor was more reliable in increasing spinal and femoral neck BMD; the Teriparatide/Abaloparatide followed by bone absorption inhibitor was more reliable in increasing spinal BMD only; and Romosozumab followed by bone absorption inhibitor was more reliable in decreasing fracture risk. Nonetheless, it is acknowledged that any collection of studies will inevitably exhibit heterogeneity. Although we performed subgroup analyses, heterogeneity remained high in some subgroups. The residual heterogeneity can be attributed to various clinical and methodological factors: (i) patient population diversity: variations in comorbidities and concomitant medications among patients influence treatment responses; (ii) disease severity and progression: differences in disease severity and progression rates lead to varied treatment outcomes, complicating the assessment of treatment response; (iii) genetic differences: genetic polymorphisms, particularly in genes related to the disease or treatment, result in variable treatment effects; (iv) external factors: diet, lifestyle, and environmental exposures also affect treatment outcomes; (v) incomplete subgroup stratification: incomplete capture of clinically relevant characteristics contributes to residual heterogeneity within subgroups; (vi) sample size: small sample sizes and imbalanced subgroup distributions affect the accuracy and generalizability of treatment effect estimates; (vii) statistical methods: model limitations fail to fully account for complex relationships between variables, leading to residual heterogeneity.

In addition, bone formation promoter drugs are expensive which can become a burden for patients. Sequential treatment increases the patient's bone density and shortens the time needed to apply bone formation promoter drugs. Furthermore, in our extensive search of existing

clinical trials, we observed a lack of clinical trials on sequential drug therapy for osteoporosis in older men, while there are more clinical trials for postmenopausal women, and therefore further research is needed in this population.

However, we must acknowledge several limitations of the present. First, the risk of bias in the blinding of participants and experimenters was considered high, which may be due to the study's reliance on long-term drug therapy studies, where open labels could not be avoided. Second, the populations included in the studies varied in terms of pre-trial anti-osteoporosis medication use, which introduced clinical heterogeneity to this study. There is also the possibility of bias due to differences in drug regimens and durations across the studies. Furthermore, although sensitivity analyses were performed to assess the stability of the results, the source of the heterogeneity was not fully understood. While subgroup analysis was conducted based on the clinical characteristics of the included studies, the limited pre-trial data may affect the reliability of the study conclusions. Finally, due to insufficient raw data, we were unable to perform a more detailed stratified analysis of clinical features within the study population, which hindered a more comprehensive evaluation of the efficacy and safety of sequential therapy with bone formation promoters followed by bone resorption inhibitors for primary osteoporosis.

Notwithstanding several limitations of our study, our evidence-based analysis has been updated to include more studies, pool additional outcome data, and conduct subgroup analyses, making our analysis more comprehensive and reliable. Our evidence-based analysis validated previous studies reporting the superiority of bone formation promoters followed by bone resorption inhibitors therapy.

Conclusion

In summary, bone formation promoters followed by bone resorption inhibitors could significantly enhance BMD at the spine, femoral neck, and total hip and reduce fracture risk for postmenopausal osteoporosis compared to monotherapy or combination therapy. However, benefits regarding the BMD at the 1/3 distal radius and the incidence of adverse events remain inconclusive. The conclusions drawn from this study still need to be further explored and validated through clinical trials with adequate sample sizes and scientifically robust study designs, including considerations to the type of osteoporosis, sex and age stratification of subjects, various drug regimens, therapy duration and diversity of outcome measures.

Abbreviations

BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
SD	Standard deviation
SMD	Standard mean difference
RANKL	Receptor activator for nuclear factor-κB ligand
RCTs	Randomized controlled trials
RR	Relative risk

Supplementary Information

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Supplementary Material 1

Author contributions

(I) Conception and design: T.L. and Y.X.L. (II) Administrative support: T.L. (III) Collection and assembly of data: Y.X.L., X.L. and Y.F.W. (IV) Data analysis and interpretation: T.L. and Y.X.L. (V) Manuscript writing: T.L. and Y.X.L. All authors contributed to the article and approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics statement

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements.

Conflict of interest

All authors declare that they have no conflict of interest.

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