ORIGINAL ARTICLE

The effects of differing resistance training modes on the preservation of bone mineral density in postmenopausal women: a meta-analysis

R. Zhao · M. Zhao · Z. Xu

Abstract

Summary This meta-analysis synthesized current evidence from 24 clinical trials to evaluate the impact of different resistance training modes on postmenopausal bone loss. Exercise interventions were categorized into two training modes, namely resistance-alone versus combined resistance training protocols. The combined resistance training protocols were defined as the combination of resistance training and high-impact or weight-bearing exercise. The results suggested that the combined resistance training protocols were effective in improving bone mineral density (BMD) at the femoral neck and lumbar spine.

Introduction The current meta-analysis aimed to examine the effects of combined resistance and resistance-alone training protocols on the preservation of femoral neck and lumbar spine BMD in postmenopausal women.

Methods An electronic database search was conducted in PubMed, EMBASE, SPORTDiscus, Web of Science, and ProQuest up to March 1, 2014 for the influence of resistance exercise on BMD in postmenopausal women. The study quality was evaluated. The effect sizes were estimated in terms of the standardized mean difference (SMD). A subgroup analysis was conducted by exercise categories.

Results Twenty-four studies were included in the overall analysis of skeletal response to resistance exercise. The between-study heterogeneity was evident for the hip ($I^2=46.5$ %) and spine ($I^2=62.3$ %). The overall analysis suggested that resistance training significantly increased femoral neck BMD (SMD=0.303, 95 % confidence interval (95 % CI)= 0.127–0.479, $p=0.001$) and lumbar spine BMD (SMD= 0.311, 95 % CI=0.115–0.507, $p=0.002$) in postmenopausal women. However, subgroup analysis indicated that combined resistance training programs significantly affected both the hip BMD (SMD=0.411, 95 % CI=0.176–0.645, $p=0.001$) and spine BMD (SMD=0.431, 95 % CI=0.159–0.702, $p=0.002$), whereas resistance-alone protocols only produced nonsignificant positive effects both on the femoral neck and lumbar spine BMD.

Conclusions Combined resistance exercise protocols appear effective in preserving femoral neck and lumbar spine BMD in postmenopausal women, whereas resistance-alone protocols only produced a nonsignificant positive effect.

Introduction

Postmenopausal women frequently suffer from persistent bone loss, increased fragility, and a high risk of fracture. Post-menopausal osteoporosis is a major public health problem in both developed and developing countries. It has been estimated that approximately 30 million American women suffered from osteoporosis in 2002, and this population is expected to expand substantially in the future [1]; in China, there were approximately 70 million osteoporotic women along with 30 million women experiencing sustained bone loss in 2006 [2]. The hip and spine are the most common sites at high risk for fracture. It has been reported that in the year 2000 there were an estimated 9.0 million osteoporotic fractures, of which 1.6 million were at the hip and 1.4 million were at the

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spine [3].Currently, compelling evidence suggests that exercise interventions have great beneficial effects on bone metabolism in older women [4, 5]. Therefore, exercise-associated improvement of bone mineral density (BMD) may be a nonpharmacological strategy for the treatment of age-related osteoporosis.

According to Frost's mechanostat theory [6], exercises producing high strain can greatly improve the mechanical properties of bone. In support of this notion, progressive high-intensity resistance training has been recognized as an effective strategy for stimulating osteogenic response and preserving BMD in older adults [7]. However, the evidence concerning effects of high-intensity resistance training on postmenopausal women BMD remains controversial [8–21]. Additionally, adaptive bone response to resistance exercise is frequently site-specific [7, 22]. A meta-analysis by Martyn-St James and Carroll [23] synthesizing a body of clinical trials with similar outcomes of interest reported that high-intensity resistance exercise was only effective in preserving postmenopausal bone loss at the lumbar spine.

To explore the optimum resistance training protocols that can best prevent postmenopausal bone loss, a large number of clinical trials with a combined design have been conducted [24–34]. Resistance training is frequently performed integrated with high-impact or weight-bearing exercise to augment the beneficial effects on BMD. These protocols are frequently termed combined resistance training protocols. Current findings have suggested that combined resistance training exercise interventions generated inconsistent results. Several lines of evidence indicated beneficial effects both at the hips [26, 29–31, 33] and spine [26, 29–31, 33, 34], whereas others either did not find positive effects or revealed negative outcomes [25, 27, 32] after combined resistance training interventions. For the inconsistent results, wide variation may exist in the sample size, training frequency, and intensity in the exercise programs. It is necessary to combine the positive and negative outcomes and employ a meta-analysis to reach general conclusions about a body of studies. The current meta-analysis aimed to examine the effects of combined resistance and resistance-alone protocols on preservation of femoral neck and lumbar spine BMD in postmenopausal women.

Methods

This meta-analysis was conducted in accordance with PRISMA recommendations and criteria for reporting of meta-analysis guidelines [35].

Search strategy

An electronic database search was conducted for the influence of resistance exercise on BMD in postmenopausal women. The included criteria are given in Table 1. Briefly, the included studies were controlled trials (CTs) or randomized controlled trials (RCTs). We included CTs in the search strategy because of the limited number of eligible studies and the long-term exercise interventions (several years) frequently available in CTs. The population of interest consisted of healthy postmenopausal women who did not perform regular exercise (less than 2.5 h per week) prior to enrollment in the study. Participants receiving hormone replacement therapy (HRT) or antiresorptive treatment (AT) were excluded. Resistance training intervention lasts for at least 6 months because bone remodeling, bone repair, and the metabolism of ions normally require approximately 6 months. Therefore, detectable skeletal responses to resistance exercise often occur after 6 months.

We searched PubMed, EMBASE, SPORTDiscus, Web of Science, and ProQuest up to March 1, 2014 for studies of the influence of resistance training on BMD in postmenopausal women. Terms used for database searches included "exercise training," "resistance exercise/training," "strength exercise/ training," "weight lifting," "weight training," "bone density," and "BMD." The search was limited to clinical trials and females (see Electronic Supplementary Material, Appendix 1).

Table 1 Criteria for inclusion of studies in the meta-analysis

Inclusion criterion	Description
Study design	Controlled or randomized controlled trials
Populations of interest	Healthy postmenopausal women without surgical experience, pharmacological treatment, or disease history affecting bone metabolism
Exercise experience	Subjects without regular exercise (less than 2.5 h per week) prior to study enrollment
Intervention	Resistance training interventions at least lasting for 6 months
Comparison	Exercise interventions compared with nonexercise control or sham exercise
Outcome measurement	The change in BMD at femoral neck and lumbar spine determined by DXA or DPA on the pre- and postexercise interventions

BMD bone mineral density, *DXA* dual X-ray absorptiometry, *DPA* dual photon absorptiometry

Data extraction

All data were extracted and reviewed independently by two authors (MZ and ZX). The details extracted included the following: subject characteristics, sample size, exercise intervention (category, intensity, frequency, and duration), attrition, compliance, HRT and AT use (not shown), regions of interest (ROIs), and BMD values with standard deviations (SDs). Studies published as multiple reports were only included once to prevent duplication in this meta-analysis.

The primary outcomes of the included trials were expressed in terms of areal BMD (BMD g/cm^2) assessed by dual X-ray absorptiometry (DXA) or dual photon absorptiometry (DPA). Absolute and relative changes in BMD from baseline to follow-up along with SDs were used for the meta-analysis. If the values of these changes were not available from the original publication or author, these were calculated using baseline and follow-up values. The data extraction followed the methods provided by the Cochrane Reviewers' Handbook [36].

Risk of bias assessment

Two authors (MZ and ZX) independently assessed the quality of the included studies using a widely utilized instrument [37]. The quality scale is a three-item questionnaire that provides an assessment of bias, specifically focusing on randomization, blinding and withdrawals. All questions are designed to elicit yes (1) or no (0) answers, and the total score ranges from 0 to 5.

Sensitivity analysis

In sensitivity analysis, we excluded five clinical trials [9, 26, 29–31] that were non-RCTs. In the five trials, the randomized assignment and blinding were not properly described. We tested, at the trial level, whether the intervention effects would be affected by excluding the five trials.

Meta-analysis

The primary endpoint was the change in BMD from baseline to follow-up at the lumbar spine or at the femoral neck. The effect sizes associated with exercise interventions were estimated in terms of the standardized mean difference (SMD). The SMD was calculated as follows:

$$\text{SMD} = \frac{X_e - X_c}{\text{SD}_{\text{pooled}}} \qquad (1)$$

where X_e represents the change score from baseline to follow-up in the exercise group, X_c represents the change score from baseline to follow-up in the control group, and $\text{SD}_{\text{pooled}}$ represents the pooled standard deviation for mean difference between the exercise and control groups.

The pooled SD was calculated from the following formula:

$$\text{SD}_{\text{pooled}} = \sqrt{\frac{(n_e-1)\text{SD}_e^2 + (n_c-1)\text{SD}_c^2}{n_e + n_c - 2}} \qquad (2)$$

where SD $_{\text{pooled}}$ is the pooled standard deviation for SMD, n_e is the sample size in the exercise group, n_c is the sample size in the control group, SD_e^2 is the square of the standard deviation in the exercise group, and SD_c^2 is the square of the standard deviation in the control group.

The SMD was chosen over the original metric because of the different ways used to describe data, for example, absolute versus relative changes in BMD. We conducted a subgroup analysis by exercise categories to determine whether different resistance training modes (combined resistance versus resistance-alone training protocols) showed different effects on BMD in elderly women. Furthermore, we used unpaired T-test to determine whether the difference in effect sizes between combined resistance and resistance-alone protocols was significant.

The intention-to-treat (ITT) approach was used in the analysis of the data. If ITT data were not available, the per-protocol approach was used in calculating the pooled effect estimates for the combination of single effects of trials. Heterogeneity of results between studies was determined using a Cochran's Q test and an alpha value of <0.10 for statistical significance. In addition, I^2 was used to examine inconsistency in the study findings. I^2 values of <25, 25 to <50, 50 to <75, and >75 % were considered to be of low, moderate, high, and very high inconsistency, respectively. The tests for the overall effects (Z-score) were considered as significant at $p < 0.05$. STATA version 12 (StataCorp LP, TX, USA) was used to perform the meta-analysis and produce the graph.
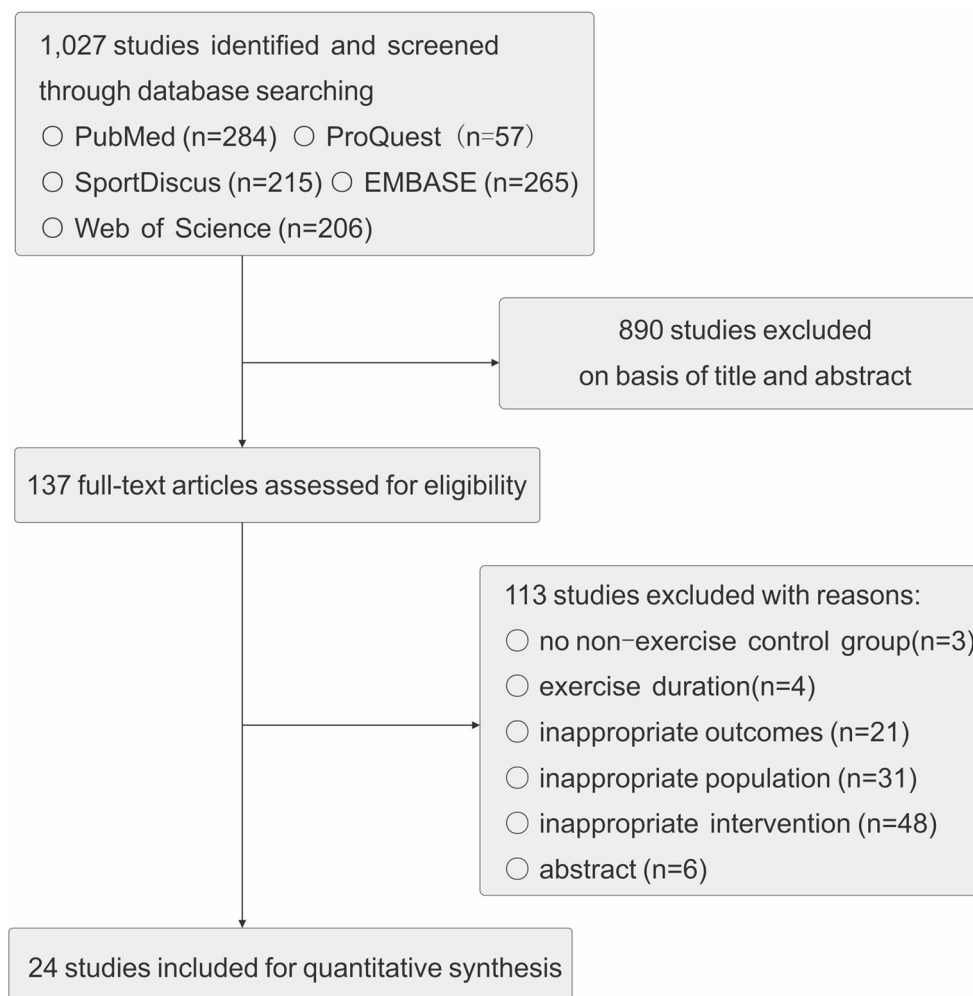
Results

Study characteristics and quality assessment

From the searches, 1027 potential abstracts were identified and screened, of which 1003 were excluded (Fig. 1). In all, 24 studies, including a total of 1769 postmenopausal women, met the inclusion criteria, among which 5 trials [9, 26, 29–31] were CTs and 19 trials [8, 10–21, 24, 25, 27, 28, 32–34] were RCTs. Four studies reported the findings of the same program, "EFOPS" [26, 29–31]. Because this was a 12-year follow-up study program and the four trials presented the results of different periods of follow-up, the four studies without duplicate data were also included in the meta-analysis according to the suggestions of the Cochrane Reviewers' Handbook [36].

All of the studies were conducted with healthy postmenopausal women between the age of 50.5±6.3 and 69.6± 4.2 years. The sample size varied from 20 to 320 participants.

Fig. 1 Flow diagram for the selection of studies

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1,027 studies identified and screened
through database searching
○ PubMed (n=284)  ○ ProQuest（n=57）
○ SportDiscus (n=215) ○ EMBASE (n=265)
○ Web of Science (n=206)
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890 studies excluded
on basis of title and abstract
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137 full-text articles assessed for eligibility
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113 studies excluded with reasons:
○ no non–exercise control group(n=3)
○ exercise duration(n=4)
○ inappropriate outcomes (n=21)
○ inappropriate population (n=31)
○ inappropriate intervention (n=48)
○ abstract (n=6)
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24 studies included for quantitative synthesis
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The studies were conducted in Canada [11, 12, 19, 25], Australia [13, 24], Brazil [10], Belgium [21], UK [15], Germany [26, 29–31, 34], and USA [8, 9, 14, 16–18, 20, 27, 28, 38]. Three studies [15, 25, 34] reported findings on the basis of the ITT approach; most clinical trials only provided per-protocol data. Descriptions of other characteristics of the participants are presented in Table 2.

Studies were awarded methodological quality points for randomization and withdrawals. No studies gained points for blinding (blinding was only used for pharmacological interventions). The quality score of the included studies was relatively low. Seven clinical trials [8, 15, 21, 24, 25, 28, 34] received a quality score of 3, 5 studies [9, 26, 29–31] received a quality score of 1, and 12 trials [10–14, 16–20, 27, 32] received a quality score of 2.

Exercise interventions

Fourteen studies prescribed resistance-alone protocols with a 10- to 20-min warm-up and a 5- to 10-min cooldown [8–21], and 10 clinical trials evaluated combined resistance exercise

protocols [24–32, 34] (Table 2). We excluded two study group comparisons [8, 18] because they used low-intensity resistance exercise. Therefore, all of the included trials were based on high-intensity resistance training. The study durations ranged from 6 months to 12 years, with a training frequency of 2–3 times per week in most interventions. With the exception of three studies [25, 33, 34] involving flexibility exercise not expected to have osteogenic effects, most participants in the control groups were asked to continue their normal dietary and physical activity habits. All of the studies measured BMD values immediately after the end of the exercise training intervention. Generally, participant compliance with the exercise interventions was relatively good, ranging from 65 to 90 %.

Meta-analysis

Overall analysis of resistance training impact on postmenopausal bone loss

Our meta-analysis pooled the data from 1769 postmenopausal women in 24 studies. A total of 924

Table 2 Characteristics of included studies

Authors [reference], country	Subject age (years) [mean±SD]	Sample size (n) [completed/dropout]	Exercise intervention	Device and ROIs	QS
Bemben et al. [8], USA	T 50.5±6.3 C 52.3±4.0	T 10/3 C 8/3	Three sets of 8 reps of 3 lower and 5 upper body resistance exercises at 80 % 1 RM. Frequency—3 days per week. Duration—6 months. Compliance: no specific information. Exercise category: resistance alone	DXA Femoral neck Lumbar spine	3
Bemben et al. [9], USA	T 64.0±0.9 C 63.1±1.4	T 22 C 12 Dropout 7	Three sets of 10 reps of 3 upper and 5 lower body exercises at 80 % 1 RM. Frequency—3 days per week. Duration—8 months. Compliance—90 %. Exercise category: resistance alone	DXA Femoral neck Lumbar spine	1
Bocalini et al. [10], Brazil	T 69.0±9.0 C 67.0±8.0	T 15/8 C 10/2	Three sets of 10 reps of upper and lower body exercises at 85 % 1 RM. Frequency—3 days per week. Duration—6 months. Compliance: no statement. Exercise category: resistance alone	DXA Femoral neck Lumbar spine	2
Bolton et al. [24], Australia	T 60.3±5.6 C 56.3±4.7	T 19/0 C 18/2	Three sets per week of resistance training, plus daily jumping and balance exercises. Frequency: 6 days per week. Duration: 12 months. Compliance: no statement. Exercise category: combined resistance training	DXA Lumbar spine	3
Chilibeck et al. [11], Canada	T 56.8±6.3 C 58.8±5.7	T 10/4 C 12/2	Two sets of 8–10 reps of 5 upper and 4 lower body exercises at 70 % 1 RM. Frequency—3 days per week. Duration—12 months. Compliance—77.6 %. Exercise category: resistance alone	DXA Femoral neck Lumbar spine	2
Chilibeck et al. [25], Canada	T 55.3±6.3 C 56.4±7.1	T 71/9 C 62/3	Two sets of strength training, plus weight-bearing exercises. Frequency—2 days per week. Duration—24 months. Compliance—77 %. Exercise category: combined resistance training	DXA Femoral neck Lumbar spine	3
Chiun et al. [12], Canada	T 65.4±3.5 C 67.4±3.8	T 11 C 7 Dropout: no statement	Three sets of 8 reps of 3 lower and 5 upper body exercises at 80 % 1 RM. Frequency—3 days per week. Duration—6 months. Compliance: no statement. Exercise category: resistance alone	DXA Femoral neck Lumbar spine	2
Engelke et al. [26], Germany	T 55.1±3.3 C 55.8±3.1	T 48/36 C 30/21	Two weekly group resistance training sessions and 2 weekly home training sessions including impact and weighted vest exercises. Frequency—4 days per week. Duration—36 months. Compliance—77 %. Exercise category: combined resistance training	DXA Lumbar spine	2
Going et al. [27], USA	T 55.8±4.7 C 57.1±5.0	T 71/20 C 59/11	Two sets of resistance training, plus weight-bearing circuit jogging, skipping, hopping, and weight vest stepping. Frequency—3 days per week. Duration—12 months. Compliance—79.9 %. Exercise category: combined resistance training	DXA Femoral neck Lumbar spine	2
Jessup et al. [28], USA	T 69.1±2.8 C 69.4±4.2	T 9/1 C 9/1	Resistance training, plus load-bearing walking, stair-climbing, and balance-training exercises. Frequency—3 days per week. Duration—8 months	DXA Femoral neck Lumbar spine	3

Table 2 (continued)

Authors [reference], country	Subject age (years) [mean±SD]	Sample size (n) [completed/ dropout]	Exercise intervention	Device and ROIs	QS
			Compliance: no statement		
			Exercise category: combined resistance training		
Kemmler et al. [29], Germany	T 55.1±3.3 C 55.8±3.1	T 59/27 C 41/10	Two weekly resistance training sessions and 2 additional training sessions including impact and weighted vest exercises Frequency—4 days per week Duration—14 months Compliance—75 %	DXA Femoral neck Lumbar spine	1
			Exercise category: combined resistance training		
Kemmler et al. [30], Germany	T 55.5±3.2 C 55.9±3.1	T 50/36 C 33/18	Two weekly joint resistance training sessions and 2 weekly home impact exercise sessions including impact and weighted vest exercises Frequency—4 days per week Duration—24 months Compliance: no statement	DXA Femoral neck Lumbar spine	1
			Exercise category: combined resistance training		
Kemmler et al. [31], Germany	T 55.1±3.3 C 55.8±3.1	T 41/45 C 44/7	Two weekly resistance training sessions and 2 additional home training sessions including impact and weighted vest exercises Frequency—4 days per week Duration—12 years Compliance: no statement	DXA Femoral neck Lumbar spine	1
			Exercise category: combined resistance training		
Kerr et al. [13], Australia	T 60.0±5.0 C 62.0±6.0	T 24/18 C 36/6	Three sets of 8 reps of 4 upper and 4 lower body resistance exercises at 8 RM Frequency—3 days per week Duration—24 months Compliance—74 %	DXA Femoral neck Lumbar spine at 12 months	2
			Exercise category: resistance alone		
Maddalozzo et al. [14], USA	T 52.3±3.3 C 52.5±3.0	T 29/6 C 29/5	Two sets of 10–12 reps of resistance exercise at 50 % 1 RM and 3 sets of 8–12 reps at 60–75 % 1 RM Frequency—2 days per week Duration—12 months Compliance—84.7 %	DXA Femoral neck Lumbar spine	2
			Exercise category: resistance alone		
Marques et al. [15], UK	T 67.3±5.2 C 67.9±5.9	T 23/8 C 24/4	Two sets of 6–8 reps of upper and lower body exercises at 80 % 1 RM Frequency—3 days per week Duration—8 months Compliance—78.4 %	DXA Femoral neck	3
			Exercise category: resistance alone		
Milliken et al. [32], USA	T/C 56.9±4.6	T 25/1 C 27/3	High-impact and aerobic weight-bearing exercises plus resistance training Frequency—3 days per week Duration—12 months Compliance: no statement	DXA Femoral neck Lumbar spine	2
			Exercise category: combined resistance training		
Nelson et al. [16], USA	T 61.1±3.7 C 57.3±6.3	T 20/1 C 19/0	Three sets of 8 reps of 3 upper and 2 lower body exercises at 80 % 1 RM Frequency—2 days per week Duration—12 months Compliance—87.5 %	DXA Femoral neck Lumbar spine	2
			Exercise category: resistance alone		
Pruitt et al. [17], USA	T 53.6±1.0 C 55.6±0.9	T 17/0 C 10/1	One set of 10 RM for upper and lower body exercises Frequency—3 days per week Duration—9 months Compliance—83 %	DPA Femoral neck Lumbar spine	2
			Exercise category: resistance alone		

Table 2 (continued)

| Authors [reference], country	Subject age (years) [mean±SD]	Sample size (n) [completed/ dropout]	Exercise intervention	Device and ROIs	QS
Pruitt et al. [18], USA	T 67.0±0.5 C 69.6±4.2	T_{HI} 8/7 C 11/1	One set of 14 reps of body exercise at 40 % 1 RM and 2 sets of 7 reps of body exercises at 80 % 1 RM. Frequency—3 days per week. Duration—12 months. Compliance—65 %. Exercise category: resistance alone	DPA Femoral neck Lumbar spine	2
Rhodes et al. [19], Canada	T 68.8±3.2 C 68.2±3.5	T 20/2 C 18/4	Three sets of 8 reps of 3 upper and 3 lower body exercises at 75 % 1 RM. Frequency—3 days per week. Duration—12 months. Compliance—85 %. Exercise category: resistance alone	DXA Femoral neck Lumbar spine	2
Smidt et al. [20], USA	T 56.6±6.6 C 55.4±8.0	T 22/3 C 27/0	Three sets of 10 reps of sit up, double leg raise, and prone trunk extension at 70 % 1 RM. Frequency—3–4 days per week. Duration—10 months. Compliance: no statement. Exercise category: resistance alone	DPA Femoral neck Lumbar spine	2
Verschueren et al. [21], Belgium	T 63.9±3.8 C 64.2±3.1	T 22/0 C 23/0	Two sets of 8–20 RM for the first 14 weeks, 1–3 sets of 8–12 RM for the last 10 weeks. Frequency—3 days per week. Duration—6 months. Compliance: no statement. Exercise category: resistance alone	DXA Femoral neck Lumbar spine	3
von Stengel et al. [34], Germany	T 68.6±3.0 C 68.1±2.7	T 45/5 C 47/4	Resistance training, plus impact and aerobic weight-bearing exercises. Frequency—4 days per week. Duration—18 months. Compliance—75 %. Exercise category: combined resistance training	DXA Lumbar spine	3

T exercise treatment group, *C* control group, *SD* standard deviation, *reps* repetitions, *RM* repetition maximal, *DXA* dual X-ray absorptiometry, *DPA* dual photon absorptiometry, *ROIs* regions of interest, *QS* quality score.

postmenopausal women completed exercise interventions; 845 control participants maintained their original daily dietary and physical activity or received flexibility exercise. Twenty-one and 23 study group comparisons with moderate ($I^2 = 46.5$ %) and high ($I^2 = 62.3$ %) levels of heterogeneity, respectively, were included in the overall analysis of the impact of resistance training on femoral neck and lumbar spine BMD in postmenopausal women. Random-effects models, which incorporated an estimate of between-study variation (heterogeneity) in the weighting, were used for calculating overall effect sizes. The findings demonstrated that resistance training interventions significantly increased femoral neck BMD (SMD=0.303, 95 % confidence interval (95 % CI)=0.127–0.479, p=0.001) (Fig. 2) and lumbar spine BMD (SMD= 0.311, 95 % CI=0.115–0.507, p=0.002) (Fig. 3) in postmenopausal women.

Different effects of combined resistance versus resistance-alone protocols on BMD

A subgroup analysis was performed to examine the different effects of combined resistance versus resistance-alone protocols on postmenopausal bone loss. Seven (I^2=48.3 %) and 10 (I^2=71.3 %) heterogeneous study group comparisons were included in the analysis of the impact of combined resistance protocols on femoral neck and lumbar spine BMD, respectively. Random-effects models were used for subgroup analysis. The findings indicated that combined resistance training protocols significantly affected both the hip BMD (SMD=0.411, 95 % CI=0.176–0.645, p=0.001) and spine BMD (SMD=0.431, 95 % CI=0.159–0.702, p=0.002) in postmenopausal women (Table 3). It was estimated that the positive effect sizes contributed to almost 1.8 and 2.4 % increment of BMD at femoral neck and lumbar spine, respectively.

Fig. 2 Forest plot for inclusion of all studies assessing changes in femoral neck bone mineral density (BMD) with resistance training. The *dotted line* represents the mean treatment effect. The *diamond* denotes overall treatment effect with 95 % confidence interval (CI). *SMD* standardized mean difference
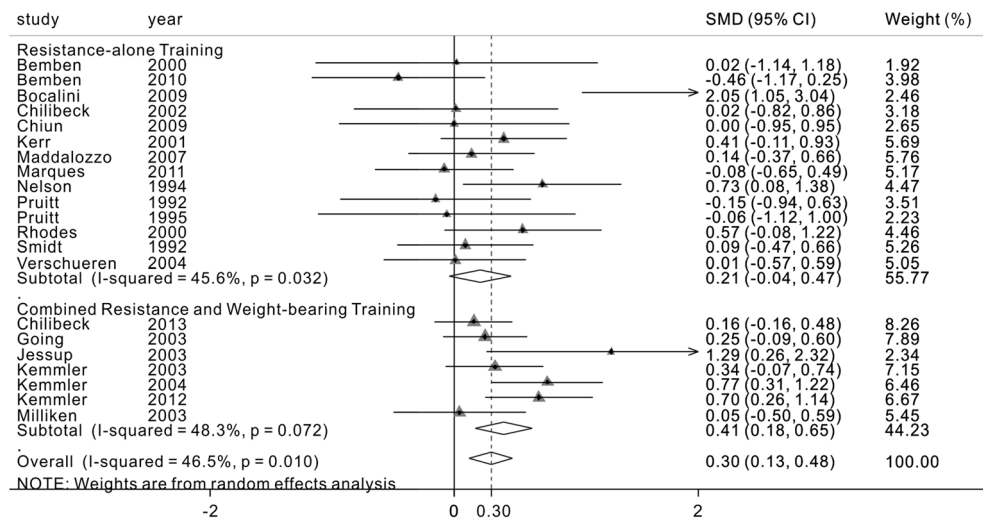
Fourteen (I^2=45.6 %) and 13 (I^2=48.3 %) moderately heterogeneous study group comparisons were included in the assessment of the influence of resistance-alone protocols on the hip and spine BMD. The results of this assessment suggested that resistance-alone protocols had no significant effects on the preservation of femoral neck BMD (SMD=0.212, 95 % CI=−0.043–0.468, p=0.104) or lumbar spine BMD (SMD=0.180, 95 % CI=−0.09–0.456, p=0.203) in postmenopausal women (Table 3).

We further determined whether the difference in effect sizes between combined resistance and resistance-alone protocols was significant. Results suggested that the difference was not statistically significant both at the hip (p=0.149) and spine (p=0.253) BMD.
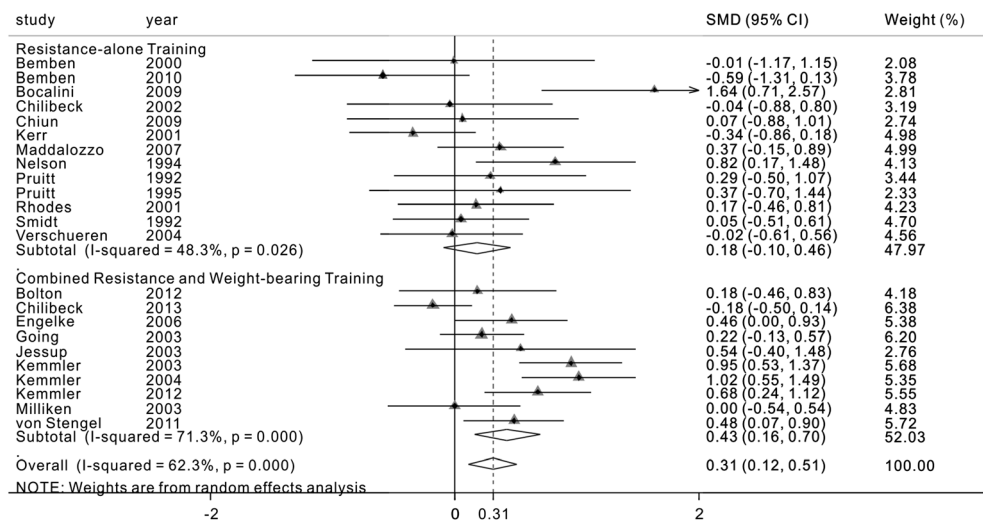
Sensitivity analysis

We determined whether the inclusion of RCTs only would affect the effect size estimates. A sensitivity analysis was conducted for 17 (I^2=36.2 %) and 18 (I^2=36.3 %) study group comparisons at the hip and spine BMD, respectively. The exclusion of five non-RCTs did not significantly alter the effect size estimates for the femoral neck BMD (SMD=0.261, 95 % CI=0.071–0.450, p=0.007) (Table 3). The intervention effects were somewhat weaker for the lumbar spine BMD (SMD=0.198, 95 % CI=0.019–0.378, p=0.030) (Table 3). The sensitivity analysis suggested that our results were relatively robust after inclusion of the five CTs in the final data analysis.

Discussion

This meta-analysis aimed to examine the effects of different modes of resistance training on femoral neck and lumbar spine BMD among postmenopausal women. Systematic searches with assessment based on the inclusion

Fig. 3 Forest plot for inclusion of all studies assessing changes in lumbar spine bone mineral density (BMD) with resistance training. The *dotted line* represents the mean treatment effect. The *diamond* denotes overall treatment effect with 95 % confidence interval (CI). *SMD* standardized mean difference

Table 3 Summary of meta-analysis, sensitivity and subgroup analyses

Analysis	Femoral neck	Lumbar spine
All included trials		
No. of studies	21	23
No. of participants		
Exercise	812	901
Control	750	821
Heterogeneity (p value)	0.010	<0.001
Inconsistency (I^2)	46.5 %	62.3 %
SMD 95 % CI	0.303 (0.127–0.479)	0.311 (0.115–0.507)
Test for overall effect (Z-score and p value)	Z=3.37, p=0.001	Z=3.11, p=0.002
All RCTs		
No. of studies	17	18
No. of participants		
Exercise	640	681
Control	620	661
Heterogeneity (p value)	0.068	0.063
Inconsistency (I^2)	36.2 %	36.3 %
SMD 95 % CI	0.261 (0.071–0.450)	0.198 (0.019–0.378)
Test for overall effect (Z-score and p value)	Z=2.70, p=0.007	Z=2.17, p=0.030
Resistance-alone protocols		
No. of studies	14	13
No. of participants		
Exercise	320	297
Control	302	278
Heterogeneity (p value)	0.032	0.026
Inconsistency (I^2)	45.6 %	48.3 %
SMD 95 % CI	0.212 (−0.043–0.468)	0.180 (−0.097–0.456)
Test for overall effect (Z-score and p value)	Z=1.63, p=0.104	Z=1.27, p=0.203
Combined resistance protocols		
No. of studies	7	10
No. of participants		
Exercise	492	604
Control	448	543
Heterogeneity (p value)	0.072	<0.001
Inconsistency (I^2)	48.3 %	71.3 %
SMD 95 % CI	0.411 (0.176–0.645)	0.431 (0.159–0.702)
Test for overall effect (Z-score and p value)	Z=3.43, p=0.001	Z=3.11, p=0.002

SMD standardized mean difference, *CI* confidence interval

criteria resulted in 24 clinical trials with a population of 1769 postmenopausal women. The overall analysis suggested that resistance exercise interventions were effective in preserving BMD at the femoral neck and lumbar spine in postmenopausal women. However, a subgroup analysis indicated that combined protocols integrating resistance training with high-impact or weight-bearing exercise were effective in improving the hip and spine BMD, whereas resistance-alone protocols only produced nonsignificant positive effects on the prevention of postmenopausal bone loss.

The effects of resistance-alone protocols on BMD

According to Frost's mechanostat theory, bone can adapt its strength to increased mechanical loading [6]. Therefore, progressive high-intensity resistance training, which usually produces a high level of mechanical strain, is expected to generate beneficial effects on postmenopausal bone health. The overall analysis suggested that the effects of resistance exercise interventions on femoral neck and lumbar spine BMD were significant (Figs. 2 and 3). Because the overall analysis included both combined resistance and resistance-alone exercise

protocols, we conducted a subgroup analysis to determine the separate effects of the two different exercise protocols on BMD in older women. Protocols that included only resistance training did not generate significant effects on BMD in older women. These results appeared to be inconsistent with the meta-analysis by Martyn-St James and Carroll in 2006 [23], which reported a significant effect on lumbar spine BMD in postmenopausal women after resistance training interventions. However, this conclusion was based on an analysis including studies that enrolled participants receiving HRT or antiresorptive agents [11, 18, 20, 33, 39]. It is known that the combination of estrogen or antiresorptive agents with exercise may generate additive or synergistic effects on skeletal response [40, 41]. Unlike Martyn-St James and Carroll's meta-analysis, our study group comparisons did not include subjects receiving pharmacological therapy. Martyn-St James and Carroll also performed a subgroup analysis that differentiated between participants receiving HRT and those not receiving HRT. After the studies with participants receiving HRT were excluded, the results suggested that high-intensity resistance training did not significantly affect either the hip or spine BMD. These results are consistent with our findings. A number of new studies have been conducted since Martyn-St James and Carroll's meta-analysis. Our meta-analysis shared eight trials with Martyn-St James and Carroll's review and included six extra trials that were not included in Martyn-St James and Carroll's study. The findings from another Cochrane analysis [42] suggested a positive response of the hip and spine BMD to high-intensity resistance training. However, it appears that that study was limited because it only included eight clinical trials in the subgroup analysis, and was unable to add substantially to the information provided by Martyn-St James and Carroll's meta-analysis [23]. Additionally, this previous meta-analysis pooled both absolute and relative change values and used mean difference (MD) methods instead of SMD to estimate the intervention effects. Therefore, the results of this previous meta-analysis might not be definitive.

The effects of combined resistance training protocols on BMD

The subgroup analysis also aimed to identify whether combined resistance training protocols would improve BMD in postmenopausal women. The findings indicated that combined resistance training protocols were effective in significantly improving the hip and spine BMD in postmenopausal women. Our findings are consistent with a meta-analysis by Martyn-St James and Carroll [43] published in 2009. In a subgroup analysis, Martyn-St James and Carroll reported that mixed loading exercise programs integrating impact activity with resistance training were effective in reducing postmenopausal bone loss at the hip and spine. However, the subgroup analysis by Martyn-St James and Carroll was limited because

it only included four trials generating five study group comparisons. Additionally, note that the participants in one study group comparison received estrogen treatment [27] and that subjects receiving HRT were also enrolled in two studies [44, 45]. The administration of estrogen may affect the skeletal response to exercise [40]. Because a number of clinical trials were conducted after this previous review, our subgroup analysis included more eligible clinical trials (11 trials) than Martyn-St James and Carroll's study. In addition, our meta-analysis focused particularly on resistance training, whereas Martyn-St James and Carroll's meta-analysis primarily concerned impact exercise. Recently, Howe et al. [42] reported in a subgroup analysis that the effects of mixed loading exercise protocols on BMD in postmenopausal women were significant at both the hip and spine. However, the results were also limited by only including six studies.

The positive training effects related to combined resistance exercise interventions have clinical significance. It was estimated that the beneficial effects induced by combined resistance training could contribute to almost 1.8 and 2.4 % BMD gains for the hip and spine in postmenopausal women. The training-related increase in BMD effectively prevented bone loss and greatly benefited postmenopausal women at risk for fracture. Current evidence demonstrates that exercise interventions are effective in fall reduction and fracture prevention [46, 47]. The overall effects could be greater considering the added benefits of exercise-related muscle mass increments, strength gained, joint flexibility and agility, and healthy dynamic movement and good balance, all of which are recognized as independent risk factors for fracture [48].

There is considerable interest in defining the optimum loading type and program to best improve bone strength so that precise exercise prescription guidelines can be developed. Evidence has shown that the skeletal response to loading is modulated by a number of different loading components, including the magnitude, rate, distribution, and number of loading cycles [49–51]. Consistent with these findings, both our meta-analysis and other studies demonstrate that the most effective programs are those involving high-impact, weight-bearing activities (jumping, skipping, dancing, and hopping) in combination with progressive high-intensity resistance training [43, 52]. However, when we directly examined the significance of the difference in the intervention effects between resistance-alone and combined resistance training protocols, the results suggested that the difference was not significant both at the hip and spine BMD. The findings seem not to support the notion that combined resistance training protocols is superior to resistance-alone training protocols for preventing postmenopausal bone loss. However, the nonsignificant results may result from the variation that exists in the sample size, population age, and exercise interventions. Additionally, the most important thing is that combined resistance training not only produces beneficial effects on BMD

in postmenopausal women, but the effects are nonsite-specific. Therefore, combined resistance training is an effective strategy for improving postmenopausal bone health. One of the main concerns in bone health practice has been whether combined resistance training is safe for older women. The number of training-related injuries reported in the included studies was very low, indicating that combined resistance training is relatively safe for older women to practice.

Currently, pharmacological treatment remains to be the standard therapy for osteoporosis, with bisphosphonates as a first line of treatment [53]. However, drug treatment only generates a modest BMD increment [54, 55] and has limited effects on the risk factors for fracture, such as weak muscle strength, reduced joint flexibility and agility, and poor dynamic movement and balance. Additionally, the long-term efficacy of pharmacological treatment may be hampered due to low compliance [56, 57], and longtime use of antiresorptive agents is likely to induce adverse effects, such as upper gastrointestinal effects [58–61]. Given that exercise usually generates beneficial effects and hardly induces side effects, combined resistance training has been regarded as a feasible strategy for preventing bone loss in postmenopausal women. However, like pharmacological treatment, low rates of adherence to exercise intervention may present a potential barrier to the improvement of postmenopausal bone health.

For the current meta-analysis, we conducted a systematic review to reduce the potential risk of bias. However, we did not present funnel plots to discuss publication bias because the subjective nature of visual interpretation of funnel plots seems to have limited use in the examination of publication bias in the current meta-analysis.

Study quality assessment and sensitivity analysis

Aspects of methodological quality including randomization, blinding, and statement on withdrawals were assessed by a widely used instrument [37]. Generally, the quality score of the included studies was relatively low. Due to the limited number of studies, we did not restrict subgroup analysis to RCTs. According to the findings of Pildal et al. [62], inadequate concealment of allocation tends to result in overestimates of intervention effects; it appeared that five studies with inadequate allocation concealment included in our meta-analysis failed to avoid this type of bias. However, a more specific meta-analysis by Wood et al. [63] found that intervention effect sizes were overestimated when inadequate sequence generation was present in trials with a subjective outcome but not in those with an objective outcome. Given that the primary outcomes in the included studies were objective measures, namely, absolute values in femoral neck and lumbar spine BMD, inadequate sequence generation may not have posed a real threat. In fact, the sensitivity analysis demonstrated that including the five CTs did not significantly alter the effect size estimates. This result indicates that the inclusion of the five CTs still yielded stable results.

In two studies [11, 25], blinding was used primarily for drug administration but not for exercise training interventions. Therefore, none of the included trials was awarded a point for blinding. It has been reported that a lack of blinding was associated with exaggerated odds ratios [62]. However, this potential bias was less for trials with objective outcomes than for those with subjective outcomes. Given the objective nature of BMD measurement, a lack of blinding in the included studies might not have posed a real threat of bias. This conclusion is important because it is difficult to conduct an exercise intervention study with a double-blinding design. Although it is possible to blind the measurer, few studies performed this type of single blinding.

Only three trials reported ITT data; most of the included studies presented results based on a per-protocol approach. An ITT analysis is preferred because it is unbiased in addressing clinically relevant research questions. The low number of clinical trials that included an ITT analysis might have induced potential bias because attrition was not considered.

Limitations

Our meta-analysis provides definitive evidence that combined resistance training protocols generate nonsite-specific effects on bone loading. The findings are clinically relevant and applicable in older women. However, our meta-analysis has inherent limitations. In all of the included studies, the measurements of BMD were made with DXA or DPA. However, these methods may not be optimal for examining bone strength. Bone can adapt both its mineral content and its structure to increased mechanical loading [39, 64, 65]. It has been reported that BMD only represents approximately 60–70 % of variation in bone strength [66]; it does not incorporate other aspects of bone quality such as microarchitecture. Therefore, BMD measurement may not be a good predictor of skeletal response to resistance training in postmenopausal women. Further detailed studies of postmenopausal women are needed to identify the material changes as well as the structural changes occurring after resistance training intervention. From a clinical perspective, these adaptive processes are important because even small changes in bone geometry and structure can significantly improve bone strength in elderly women. Our meta-analysis was also limited because the data represented highly selected samples of postmenopausal women of varying ages. Additionally, the relatively low quality of the included studies was also a limitation in our meta-analysis. As we included four studies that reported the findings of the same program, "EFOPS," a 12-year follow-up study, the use of these studies in the meta-analysis might potentially impact the results of pooling intervention effects.

Conclusions

The general conclusions of the present meta-analysis were that progressive high-intensity resistance training tended to be effective for improving or preserving hip and spine BMD in postmenopausal women. However, skeletal adaptation was dependent on training modes, as the combined protocols that integrated resistance training with high-impact or weight-bearing exercises showed significant beneficial effects on postmenopausal bone loss, while resistance-alone protocols did not. Although the number of training-related injuries reported in the included studies was very low, caution is advised when resistance training is performed at home or without supervision because the resistance exercise conducted by the participants in the clinical trials was usually performed with special training equipment and under supervision. The poor quality of several trials reminds us that well-designed studies with large sample sizes are still needed. Further studies are also needed to characterize both material and structural changes to determine exercise-induced gains in bone strength. Nevertheless, combined resistance training protocols furnish a feasible nonpharmacological strategy for preventing postmenopausal bone loss.

Conflicts of interest None.

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