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Meta-analysis of walking for preservation of bone mineral density in postmenopausal women

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ABSTRACT

Whilst exercise is recommended for optimum bone health in adult women, there are few systematic reviews of the efficacy of walking as singular exercise therapy for postmenopausal bone loss. The aim of this study was to assess the effects of prescribed walking programmes on bone mineral density (BMD) at the hip and spine in postmenopausal women and to determine if effects are modified by variations in protocol design. We undertook a systematic review and meta-analysis of randomised (RCTs) and non-randomised controlled trials. Electronic bibliographic databases, key journals and reference lists of reviews and articles were searched to identify studies for inclusion. Randomised and non-randomised controlled trials assessing the effects of walking on lumbar spine, femoral neck and total hip BMD, measured by radiographic techniques, among sedentary postmenopausal women were eligible for inclusion. Two independent reviewers assessed studies for eligibility. Reported absolute BMD outcomes were combined in the analysis. Weighted mean differences (WMD) were calculated using a fixed and random-effects models. Heterogeneity among trials was examined using the Q statistic and I^2 methods. Potential publication bias was assessed through funnel plot inspection. Assessment of trial quality was also performed using the widely used instrument devised by Jadad et al. [Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Cont Clin Trials 1996; 17:1–12].

Eight trials were eligible for inclusion. Treatment duration ranged from 6 to 24 months. All eight trials reported BMD data at the lumbar spine following walking interventions among postmenopausal women. Meta-analysis showed no significant change in BMD at this site [WMD (fixed-effect) 0.007 g/cm^2 95% CI (−0.001 to 0.016); P=0.09)]. BMD data at the femoral neck were available from five trials among postmenopausal women. Results were inconsistent (I^2=51.4%) in showing a positive effect of walking on BMD at this site [WMD (random-effects) 0.014 g/cm^2 95% CI (0.000 to 0.028); P=0.05). Insufficient data were available for meta-analysis of the total hip site. Funnel plots showed some asymmetry for negative lumbar spine BMD outcomes. Trial quality scores ranged from 0 to 3 from the Jadad scale of 0 to 5.

We conclude that regular walking has no significant effect on preservation of BMD at the spine in postmenopausal women, whilst significant positive effects at femoral neck are evident. However, diverse methodological and reporting discrepancies are apparent in the published trials on which these conclusions are based. Other forms of exercise that provide greater targeted skeletal loading may be required to preserve bone mineral density in this population.

Introduction

Osteoporosis increases the risk of fractures among elderly postmenopausal women [2]. Hip and spine fractures are associated with high morbidity and mortality in this population [3,4]. Regular physical activity is promoted as having a positive influence on quality of life, morbidity and mortality in older adults [5]. However, guidelines and position stands that have reviewed the evidence for the effects of exercise on bone health in women have reached different conclusions regarding exercise for bone augmentation [2,6,7].

The American College of Sports Medicine (ACSM) position stand on physical activity and bone health recommends regular weight-bearing endurance activities in conjunction with resistance activities for preserving bone mass in elderly women [6]. The ACSM position stand evaluates walking programmes as only conferring modest effects on bone mass in older women. However, this expert opinion is based on only two walking studies [8,9].

An early meta-analysis of the effects of exercise programmes on bone mass in postmenopausal women, synthesising walking with

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other exercise interventions, observed significant effects at the spine, but not hip [10]. A recent systematic review of exercise effects in postmenopausal women [7], reported walking to have favourable effects on bone density based on two RCTs [11,12]. In their Cochrane systematic review Bonaiuti et al. [13] showed walking to significantly increase BMD at both the spine and the hip from meta-analysis of RCTs in postmenopausal women. Conversely, Palombaro [14] found walking to have a significant, but small, positive effect on lumbar spine BMD but not on femoral neck.

The purpose of the present study is to critically evaluate and report, through systematic review and meta-analysis, the effects of walking interventions on hip and spine BMD in postmenopausal women reported in randomised and non-randomised controlled trials.

Methods

We carried out our meta-analysis in line with Cochrane Collaboration recommendations and quality of reporting of meta-analyses guidelines [15,16]. The recommendations made by the Cochrane Musculoskeletal Group for improvements in systematic reviews of therapies for musculoskeletal conditions were also considered prior to undertaking this review and applied where appropriate [17].

Systematic searches of the following databases from their inception to end December 2006 were undertaken: MEDLINE (1966), EMBASE (1980), PubMed (1966), Web of Science (1945), Sports Discus (1975), EBMZ (1917), and ProQuest (1995). Text words, key words and subject headings used in the searches included: women or females; walking, exercise, physical therapy or physical activity; bone density, bone mineral density or bone mass; osteoporosis or osteopenia; and clinical trial, controlled trial or randomised controlled trial. Additional references from 1986 to end December 2006 were searched manually in selected peer-reviewed journals (*Bone, Calcified Tissue International, Journal of Bone and Mineral Metabolism, Journal of Bone and Mineral Research, Osteoporosis International, and Medicine and Science in Sports and Exercise*); along with reference lists of other exercise reviews in the area [13,14,18,19], reference lists of articles identified for inclusion, and Web searches (www.scholar.google.com). Citations were entered into reference management software (Reference Manager version 11, Thomson ResearchSoft, Carlsbad, Calif.).

Studies reported as peer-reviewed articles, abstracts, theses and dissertations were eligible for inclusion, as were studies published in languages other than English. Only study groups enrolling postmenopausal women from controlled trials of walking interventions were included. Where publications were by the same institution, group or author, clarity regarding whether BMD data from the same study population was reported in more than one trial was sought. Where trials reported BMD data for the same participants in more than one publication, data from only one of the publications were included to avoid double counting participants in the meta-analysis [20].

Participants were defined as sedentary postmenopausal women. Trials recruiting female samples drawn from active populations such as aerobics or fitness classes, where the loading characteristics of participants' physical activity could already have augmented BMD were excluded. Treatment groups comprising men only were excluded as were treatment groups including both men and women where data for the women only were not presented or provided when requested from the author.

The intervention of interest was walking alone as the sole exercise treatment. Treatment groups investigating the effects of walking combined with other forms of skeletal loading exercise were excluded.

Outcomes for this review were defined as BMD at the lumbar spine, femoral neck and total hip. Trials were included that provided either absolute change from baseline or follow-up values in areal bone mineral density (BMD g/cm^2) measured by radiographic techniques (single photon absorptiometry — SPA, dual photon absorptiometry — DPA, or dual X-ray absorptiometry — DXA). BMD values (g/cm^2) with standard deviations (SD) were used in the meta-analysis. Relative changes (%) in BMD were also extracted and analysed for comparative purposes.

Data were extracted from each article independently by two reviewers (MMSJ and SC). Details abstracted included: participant characteristics, numbers of allocated participants and number of participants followed-up; length of treatment, attrition, compliance, exercise supervision; any adjuvant pharmacological or nutritional therapy affecting bone that participants were either already taking or had been prescribed to them as part of the intervention; region of interest (ROI) assessed, scanning technique used, and BMD values with standard deviations (SD). There was no disagreement between reviewers regarding the eligibility of studies identified for inclusion.

In order to include trials with more than one treatment arm (for example different walking intensities) but only one control group, each treatment group was included separately within the meta-analysis, but with the control group participant number divided out equally between the comparisons. This process ensures that control participants are not counted more than once within the meta-analysis [20].

Given that BMD values are continuous data, the weighted mean difference (WMD) method was used for combining study effect size estimates. In this method the pooled effect estimate represents a weighted average of all included study group comparisons. Weighting assigned to each individual study group comparison result in the analysis is in inverse proportion to the variance. This method assigns more weight in the meta-analysis to larger trials and less weight to the smaller ones [21]. Weighted mean differences (WMD) were calculated using fixed-effect and random-effects models.

Heterogeneity of net study group changes in BMD was examined using the Q statistic. Cochran's Q statistic is computed by summing the squared deviations of each trial's estimate from the overall meta-analytic estimate, weighting each trial's contribution in the same manner as in the meta-analysis. P values are obtained by comparing the statistic with a chi^2 distribution with $k-1$ degrees of freedom (where k is the number of trials). A P value of <0.10 was adopted since the Q statistic tends to suffer from low differential power [22]. The formal Q statistic was used in conjunction with recently proposed methods (I^2) for assessing heterogeneity.[22] The statistic I^2 measures the extent of inconsistency among the trials' results, interpreted as approximately the proportion of total variation in trial estimates that is due to heterogeneity rather than sampling error [22].

Effect sizes with a corresponding I^2 value of ≤50% were considered homogenous in the present meta-analysis. A random-effects model was used to further analyse results which were determine to be heterogeneous ($I^2>50\%$) [23]. Heterogeneity was further explored by conducting subgroup analyses. For comparative purposes both fixed-effect and random-effects outcomes for all analyses are reported. Tests for overall effect were considered significant at $P<0.05$.

Subgroup analyses were defined *a priori* to investigate differences in the magnitude of treatment effects across studies due to variations in protocol. These were hypothesised to be additional effects of hormone therapy use among participants or nutritional supplementation prescribed to study participants as a co-intervention, and differences due to differing devices used to assess BMD. Sensitivity analyses were also undertaken to assess aspects of study quality including randomisation and attrition.

Publication bias was examined through funnel plot inspection [20]. Funnel plots provide a scatter plot of the treatment effects of included trials against a measure of the trial's sample size. In the absence of bias, the plot should resemble an inverted symmetrical funnel. Visual inspection of funnel plots provides a generic and accepted method to assess publication bias in meta-analysis [20].

Meta-analysis and production of all graphics were performed using RevMan version 5 (Cochrane Collaboration).

An assessment of trial quality was undertaken for comparative purposes using the questionnaire described by Jadad et al. [1]. This is a three-item instrument that provides an assessment of bias, specifically randomisation, blinding and withdrawals/dropout. All questions are designed to elicit yes (1 point) or no (0 point) answers. The total number of points available ranges from 0 to 5. The instrument awards a maximum of 2 points for randomisation, a maximum of 2 points for blinding, and a maximum of 1 point for withdrawals/dropout.

Results

From the searches, 169 exercise studies were identified for potential inclusion and full-text versions obtained (Fig. 1). Thirty-six of the studies evaluated walking interventions. Twenty-seven walking trials did not meet all inclusion criteria for this review and were excluded. Reasons for exclusion are given in Fig. 1. Eight walking trials compared walking as a singular exercise treatment with a non-exercise control group and reported BMD outcomes assessed by radiographic techniques at the hip and/or spine in postmenopausal women and were included (Table 1) [9,11,12,24–28]. Study group allocation was reported as randomised in five of the included trials [11,12,24–27]. Details of all excluded studies are available from the author.

Participant characteristics

Participants recruited were predominantly Caucasian [9,11,24–26], or Japanese. [12,27,28]. Reported years postmenopause was variable ranging from approximately 4 to 20 years (Table 1).

Pharmacological therapy use

Seven of the trials either excluded hormone replacement therapy (HRT) use among participants, or reported that none of the included participants was taking it [9,11,12,25–28] (Table 1). One trial reported recruiting four participants already receiving HRT who were assigned equally to walking and control groups [24] (Table 1).

Supervision and compliance

Details regarding supervision of the walking programmes were reported in seven of the trials [9,11,24–28], of which three reported that all walking sessions were supervised [9,25,27], and one reported that, apart from the assessment sessions, participants were unsupervised [11] (Table 1). Compliance with the prescribed walking interventions as a percentage of sessions attended was reported on in only two trials [9,25] where it ranged from 77% to 85% (Table 1).

Concurrent supplementation

Two trials were factorially designed to also assess nutritional supplementation effects on BMD as a co-intervention with walking [9,27]. One trial allocated participants to four study groups, integrating calcium versus placebo with walking versus control [9] (Table 1). Another randomised participants to four study groups of isoflavone versus placebo combined with walking versus control [27] (Table 1). One trial reported increasing all control and treatment participants' daily calcium intake for the duration of the intervention [26] (Table 1).

BMD assessment

Duration of the included trials was variable with final BMD assessment ranging from 6 to 24 months. Three trials reported ongoing BMD assessment at varying timepoint points [24,26,28]. Final follow-up was at 12 months in two of these trials [26,28], and at 24 months in the other [24]]. All other trials reported single final BMD follow-ups (Table 1).

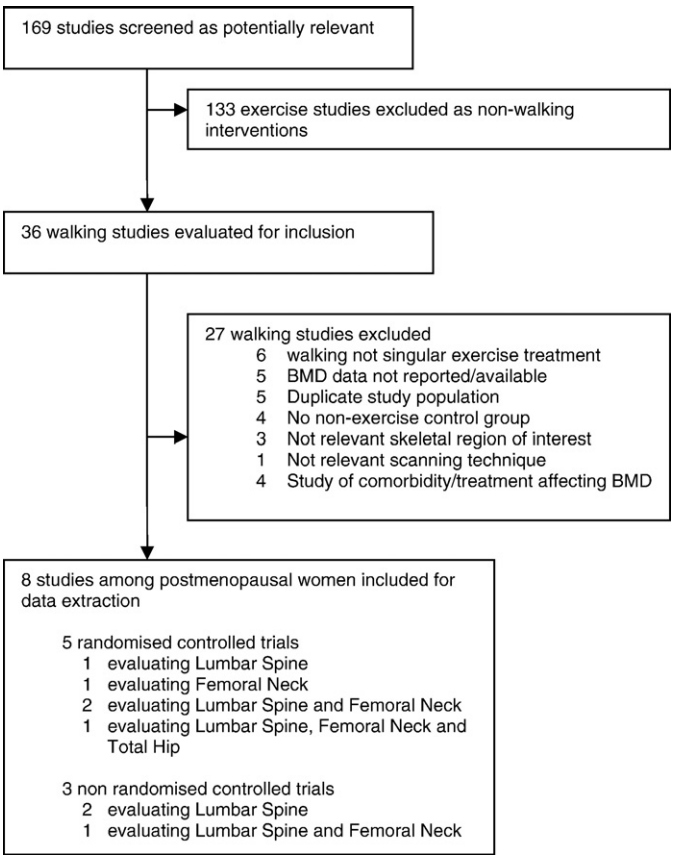

Fig. 1. Study selection process.

BMD at lumbar spine was assessed in eight trials [9,11,12,24–28], and femoral neck BMD was also assessed in five of these [9,11,24,25,27] (Table 1). Total hip BMD was assessed in only one of the trials [27] and therefore no meta-analysis for this ROI was undertaken. Table 2 summarises all meta-analysis comparisons undertaken.

Four of the trials assessed BMD using DXA equipment [12,24,27,28], and the remaining 4 used DPA equipment [9,11,25,26].

Attrition

Loss to follow-up (participant assigned versus those completing end-point assessment) was reported in all trials (Table 1). High attrition (41% of participants withdrawing) was noted in one trial [24].

Quality assessment score

The quality assessment instrument scores awarded to trials ranged from 1 to 3 (Table 1) from a scale of 0 to 5 [1]. In addition to one point for randomisation, only one RCT was allocated an extra point for including a description of an appropriate randomisation method [24]. Only one of the included trials acquired a total quality score of three [24]. No trial gained points for blinding of participants or contained a description of adequate concealment of allocation.

Meta-analysis

All of the eight included trials assessed lumbar spine BMD and provided 12 study group comparisons of walking versus control. A total

Table 1
Details of controlled trials of walking effects on BMD

Source	Brooke–Wavell et al. [11]	Ebrahim et al. [24]	Hatori et al. [12]	Little [25]	Martin and Notelovitz [26]	Nelson et al. [9]	Wu et al. [27]	Yamazaki et al. [28]
Design	Randomised controlled trial	Randomised controlled trial	Controlled trial	Randomised controlled trial	Randomised controlled trial	Controlled trial	Randomised controlled trial	Controlled trial
Country	UK	UK	Japan	America	America	America	Japan	Japan
Duration (months)	12	24	7	8	12	12	6	12
No. of participants assigned								
Walking	43	81	Groups 1 and 2, 23	7	Group 1, 27 Group 2, 25	Walking and control group 1, 21 Walking and control group 2, 20	Group 1, 34 Group 2, 34	32
Control	41	84	12	4	24		Group 1, 34 Group 2, 34	18
Mean age (range)	65 (60–70)	67	57 (45–67)	55.8	58	60	55 (45–60)	65 (49–75)
HRT use	Women taking HRT were excluded	Some HRT users (*n*, 4) included	No HRT users included	No HRT users included	No HRT users included	Women not taking HRT included	Women not taking HRT included	Women not taking HRT included
Smoking	8 smokers included	Smoking habits not reported	Smoking habits not reported	Non-smokers	Non-smokers	Smoking habits not reported	Non-smokers	Non-smokers
Years since menopause						All participants 10.8±1.2		
Walking	15.1±5.5	approx 20.0	Not reported	3.9±2.2	15.3±10.5		Group 1, 3.6±1.8 Group 2, 34	16.6±1.7
Control	15.1±5.5	approx 18.0	Not reported	8.4±1.5	10.2±84		Group 1, 3.7±2.1 Group 2, 3.2±1.4	14.6±1.6
Walking intervention	20–50 min continuous self-selected brisk pace	40 min self-paced brisk walking	Group 1, 30 min low intensity walking on grass Group 2, 30 min high-intensity walking on grass	20–30 min continuous walking	Group 1, graded treadmill for 30 min Group 2, graded treadmill for 40 min	Groups 1 and 2, 50 min walking at 75–80% HRmax (wearing 3.1 kg weighted belt after 4 wk)	Groups 1 and 2, 45-min walking at 5–6 kph	Daily outdoor walking at 50% VO2max of at least 1 h/d

Frequency per week	2.5 h/wk	3 d/wk	3 d/wk	3 d/wk	3 d/wk	3 d/wk	3 d/wk	At least 4 d/wk
Supervision	Most sessions unsupervised	Unsupervised	No statement on supervision	All sessions supervised	No statement on supervision	All sessions supervised	All sessions supervised	Unsupervised
Nutritional supplementation	None	None	None	None	All participants given calcium 1000 mg/d	Walking and control group 1 given calcium 831 mg/d Walking and control group 2 given placebo	Walking and control group 1 given soy isoflavones, 75 mg/d Walking and control group 2 given placebo	None
Regions of interest assessed	Lumbar spine Femoral neck	Lumbar spine Femoral neck	Lumbar Spine	Lumbar spine Femoral neck	Lumbar Spine	Lumbar Spine Femoral Neck	Lumbar Spine Femoral Neck Total Hip	Lumbar Spine
Device (manufacturer)	DPA (Lunar)	DXA (Lunar)	DXA (Hologic)	DPA (Lunar)	DPA (Lunar)	DPA (Lunar)	DXA (Hologic)	DXA (Norland)
No. of participants assessed								
Walking	38	49	Group 1, 11 Group 2, 9	6	Group 1, 20 Group 2, 16	Group 1, 9 Group 2, 9	Group 1, 31 Group 2, 31	27
Control	40	48	12	4	19	Group 1, 9 Group 2, 9	Group 1, 33 Group 2, 33	15
Compliance %	Not reported, average 20.4± 3.8 min/day	Not reported	Not reported	85%	77–85% of training sessions attended	Not reported, mean attendance >90%	Not reported, mean no. steps at 6 months reported	Not reported, mean daily step count reported
Trial quality score								
Study described as randomised:	1	1	0	1	1	0	1	0
Method appropriate (+1)	0	1	0	0	0	0	0	0
Inappropriate (−1)	0	0	0	0	0	0	0	0
Described as double-blind	0	0	0	0	0	0	0	0
Method appropriate (+1)	0	0	0	0	0	0	0	0
Inappropriate (−1)	0	0	0	0	0	0	0	0
Description of withdrawals	1	1	1	1	1	1	1	1
Total (out of 5)	2	3	1	2	2	1	2	1

Table 2
Summary of meta-analyses, sensitivity and subgroup analyses by region of interest

Analysis	Lumbar spine		Femoral neck	
	Fixed-effect	Random-effects	Fixed-effect	Random-effects
All included trials				
No. of study group comparisons	12		7	
No. of participants				
Walking	247		171	
Control	180		131	
Heterogeneity (*P* value)	0.55		0.05	
Inconsistency (I^2 value)	0%		51.4%	
WMD (g/cm^2) 95% confidence interval	**0.007 (−0.001 to 0.016)**	0.007 (−0.001 to 0.016)	0.012 (0.003 to 0.020)	**0.014 (0.000 to 0.028)**
Test for overall effect (*Z* score and *P* value)	**1.70 (0.09)**[a]	1.70 (0.09)	2.75 (0.01)	**1.99 (0.05)**[a]
Randomised controlled trials (RCTs) only				
No. of study group comparisons	7		5	
No. of participants				
Walking	191		155	
Control	144		123	
Heterogeneity (P value)	0.27		0.49	
Inconsistency (I^2 value)	21.1%		0%	
WMD (g/cm^2) 95% confidence interval	**0.006 (−0.004 to 0.016)**	0.001 (−0.015 to 0.017)	**0.012 (−0.001 to 0.026)**	0.012 (−0.001 to 0.026)
Test for overall effect (*Z* score and *P* value)	**1.25 (0.21)**[a]	0.09 (0.93)	**1.87 (0.06)**[a]	1.87 (0.06)
Trials with <30% attrition				
No. of study group comparisons	11		6	
No. of participants				
Walking	198		122	
Control	132		83	
Heterogeneity (*P* value)	0.52		0.04	
Inconsistency (I^2 value)	0%		57.8%	
WMD (g/cm^2) 95% confidence interval	**0.009 (0.000 to 0.018)**	0.009 (0.000 to 0.018)	0.011 (0.001 to 0.020)	**0.014 (−0.004 to 0.031)**
Test for overall effect (*Z* score and *P* value)	**1.87 (0.06)**[a]	1.87 (0.06)	2.27 (0.02)	**1.56 (0.12)**[a]
RTCs with <30% attrition				
No. of study group comparisons	6		4	
No. of participants			4	
Walking	142		106	
Control	96		75	
Heterogeneity (*P* value)	0.21		0.41	
Inconsistency (I^2 value)	30.3%		0%	
WMD (g/cm^2) 95% confidence interval	**0.008 (−0.003 to 0.019)**	−0.014 (−0.048 to 0.021)	**0.009 (−0.008 to 0.025)**	0.009 (−0.008 to 0.025)
Test for overall effect (*Z* score and *P* value)	**1.41 (0.16)**[a]	0.78 (0.43)	**1.06 (0.29)**[a]	1.06 (0.29)
Trials including HRT users	N/A		N/A	
Trials assessing walking without nutritional co-intervention				
No. of study group comparisons	10		5	
No. of participants				
Walking	208		131	
Control	159		111	
Heterogeneity (*P* value)	0.51		0.26	
Inconsistency (I^2 value)	0%		24.2%	
WMD (g/cm^2) 95% confidence interval	**0.008 (−0.001 to 0.017)**	0.008 (−0.001 to 0.017)	**0.005 (−0.004 to 0.015)**	0.007 (−0.006 to 0.019)
Test for overall effect (*Z* score and *P* value)	**1.82 (0.07)**[a]	1.82 (0.07)	**1.06 (0.29)**[a]	1.07 (0.28)
Trials assessing BMD with DPA				
No. of study group comparisons	6		4	
No. of participants				
Walking	97		60	
Control	72		50	
Heterogeneity (*P* value)	0.27		0.01	
Inconsistency (I^2 value)	22.0%		73.7%	
WMD (g/cm^2) 95% confidence interval	**0.008 (−0.003 to 0.019)**	−0.007 (−0.039 to 0.024)	0.011 (0.001 to 0.020)	**0.015 (−0.006 to 0.036)**
Test for overall effect (*Z* score and *P* value)	**1.51 (0.13)**[a]	0.46 (0.65)	2.23 (0.03)	**1.42 (0.16)**[a]
Trials assessing BMD with DXA				
No. of study group comparisons	6		3	
No. of participants				
Walking	150		111	
Control	108		81	
Heterogeneity (*P* value)	0.67		0.76	
Inconsistency (I^2 value)	0%		0%	
WMD (g/cm^2) 95% confidence interval	**0.006 (−0.008 to 0.020)**	0.006 (−0.008 to 0.020)	**0.017 (−0.002 to 0.037)**	0.017 (−0.002 to 0.037)
Test for overall effect (*Z* score and *P* value)	**0.85 (0.40)**[a]	0.85 (0.40)	**1.73 (0.08)**[a]	1.73 (0.08)

Table 2 (*continued*)

Analysis	Lumbar spine		Femoral neck	
	Fixed-effect	Random-effects	Fixed-effect	Random-effects
Relative (%) change — all included trials				
No. of study group comparisons	12		7	
No. of participants				
Walking	247		171	
Control	180		131	
Heterogeneity (*P* value)	0.02		0.60	
Inconsistency (I^2 value)	53%		0%	
WMD (g/cm^2) 95% confidence interval	0.06 (−0.52 to 0.64)	**0.39 (−0.57 to 1.34)**	**0.35 (−0.38 to 1.08)**	0.35 (−0.38 to 1.08)
Test for overall effect (*Z* score and *P* value)	0.21 (0.84)	**0.79 (0.43)**[a]	**0.95 (0.34)**[a]	0.95 (0.34)
Relative (%) change — randomised controlled trials (RCTs) only				
No. of study group comparisons	7		5	
No. of participants				
Walking	191		155	
Control	144		123	
Heterogeneity (*P* value)	0.20		0.80	
Inconsistency (I^2 value)	30%		0%	
WMD (g/cm^2) 95% confidence interval	**−0.29 (−0.91 to 0.33)**	−0.22 (−1.00 to 0.57)	**0.35 (−0.59 to 1.30)**	0.35 (−0.59 to 1.30)
Test for overall effect (*Z* score and *P* value)	**0.79 (0.43)**[a]	0.54 (0.59)	**0.73 (0.46)**[a]	0.73 (0.46)

Bold: Test for overall effect from model applied according to observed heterogeneity from I^2 value.
[a] Test for overall effect from model applied according to observed heterogeneity from I^2 value.

of 247 participants were assigned to walking intervention and 180 to control. Meta-analysis including all study groups was homogenous (I^2=0%) for effects of walking on BMD at this site. The combined weighted mean difference (WMD) in BMD was 0.007 g/cm^2 [WMD (fixed-effect) 95% confidence interval [CI], −0.001 to 0.016; *P*=0.09)]. The relative change in lumbar spine BMD was 0.39% [(I^2=53%); WMD (random-effects) 95% confidence interval [CI], −0.57 to 1.34; (*P*=0.43)].

The five trials that assessed femoral neck BMD provided seven study group comparisons totalling 171 treatment participants and 131 controls. Heterogeneity of study effects was observed in this analysis (I^2=51.4%). Among these study groups walking interventions resulted in an increase in BMD at this site of 0.014 g/cm^2 [WMD (random-effects) 95% confidence interval [CI] (0.000 to 0.028); *P*=0.05]. The relative change in femoral neck BMD was 0.35% [(I^2=0%); WMD (fixed-effects) 95% confidence interval [CI], −0.38 to 1.08; (*P*=0.34)]. Table 2 lists results from all meta-analyses, sensitivity and subgroup analyses.

Sensitivity analysis including only trials of random design (RCTs) did not show any significant differences at either lumbar spine or femoral neck. Seven RCT study group comparisons [11,24–27] assessing lumbar spine BMD were homogenous (I^2=21.1%). The WMD in BMD at this site was 0.006 g/cm^2 [(fixed-effect) 95% confidence interval [CI], −0.004 to 0.016; *P*=0.21]. The analysis of the five RCT study groups assessing femoral neck BMD [11, 24, 25, 27] was also homogenous (I^2=0%). The WMD in BMD among RCT study groups at this site was 0.012 g/cm^2 [(fixed-effect) 95% confidence interval [CI], −0.001 to 0.026; *P*=0.06]. Figs. 2 and 3 show the results from meta-analysis of all included RCTs.

Lack of treatment effect at both the lumbar spine and femoral neck was also confirmed in sensitivity analysis excluding trials with high attrition (>30%). Subgroup analyses for the potential effects of participants already using HRT could not be undertaken as only one trial reported including HRT users [24]. The subgroup analyses excluding trials with nutritional co-interventions were consistent in showing no significant effects of walking on BMD at either lumbar spine or femoral neck (I^2=0% and I^2=24.2%, respectively). No significant effects in BMD were evident at either lumbar spine or femoral neck when study group comparisons were meta-analysed according to scanning device (DPA or DXA).

Funnel plots were produced for the effects of walking interventions on lumbar spine BMD from all included RCTs (Fig. 4). Similar plots were also produced for femoral neck outcomes (Fig. 5). Visual inspection of these plots indicated a greater number of trials demonstrating a negative treatment effect on lumbar spine BMD, whereas for femoral neck outcomes were more equally distributed within the 95% confidence interval lines.

Discussion

The primary purpose of this study was to undertake a systematic review of trials assessing the effects of walking on bone mineral

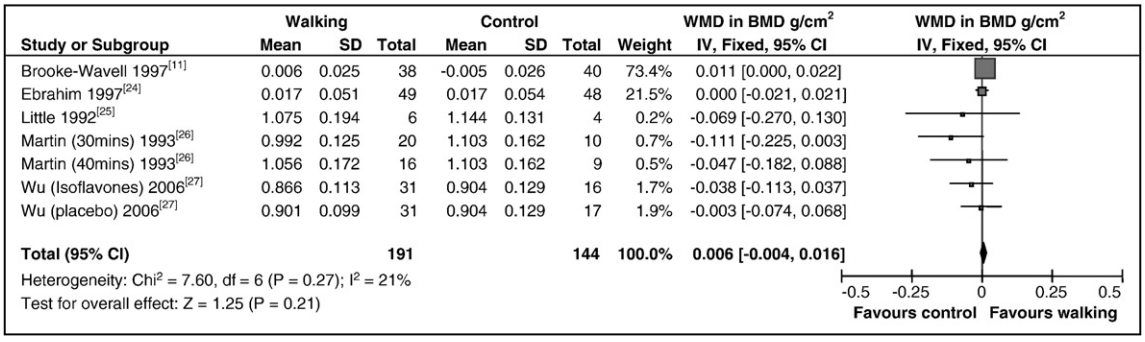

Fig. 2. Forest plot for RCT effects of walking on lumbar spine bone mineral density.

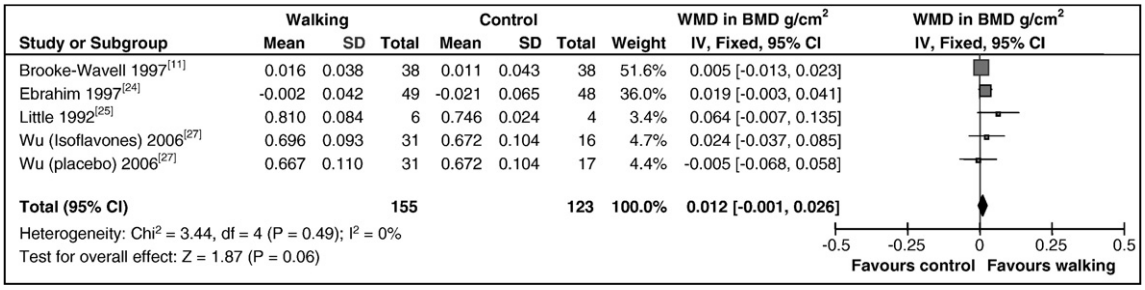

Fig. 3. Forest plot for RCT effects of walking on femoral neck bone mineral density.

density (BMD) at the hip and spine in postmenopausal women. The second purpose was to undertake a meta-analysis of BMD outcomes at these skeletal regions of interest. Data were included from study group comparisons comprised of postmenopausal women where walking alone was the only exercise intervention prescribed to treatment groups. Our findings indicate that the published trials in this area do not support the efficacy of walking as a singular exercise intervention for preserving bone mineral density at the lumbar spine or femoral neck in postmenopausal women.

We included both randomised and non-randomised trials reported in peer-reviewed journals, dissertations or abstracts. It has been noted that trials employing random allocation methods will yield more conservative results compared with non-random allocation methods [29]. In one of the earliest meta-analyses of exercise effects on bone in women, Wolff et al. [19] observed that RCTs showed a modest effect at both lumbar spine and femoral neck whilst non-random trials over-estimated treatment effects. Our results are comparable to those observed by Wolff et al. [19]. Our initial analyses incorporating all trials meeting inclusion criteria found positive effect estimates at both the lumbar spine and femoral neck. Restricting the analyses to RCTs only resulted in non-significant findings.

In their Cochrane review of exercise for osteoporosis, Bonaiuti et al. [13] included only RCTs evaluating exercise effects on BMD, meta-analysing results from three walking trials assessing lumbar spine [12,24,26]. However, we note that in one of these trials only the treatment arms were randomised [12]. In contrast to our findings, the meta-analysis results of Bonaiuti et al. [13] indicate a significant effect of walking on BMD at lumbar spine. However, their analysis did not include all of the available treatment group comparisons from two of the trials [12,26]. In one [12], only the higher intensity walking group comparison was included and in the other [26], only the longer duration session group was included. When we excluded the same 2 study group comparisons (lower intensity [12], and shorter duration [26]) from our lumbar spine meta-analysis, a non-significant (P=0.07) increase in BMD of 0.008 g/cm^2 was observed at this site (meta-analysis not presented).

Bonaiuti et al. [13] also observed significant positive effects of walking on femoral neck BMD from meta-analysis of study group comparisons from just two RCTs [30,31]. We excluded these trials from our review as walking was either additional to attendance at exercise classes [31], or part of an exercise class that also included aerobic dance [30].

The meta-analyses of Bérard et al. [10] and Palombaro [14] used similar methodologies yet Bérard et al. [10] found larger effect sizes at lumbar spine compared with Palombaro [14]. However, the earlier meta-analysis of Bérard et al. [10] synthesised walking interventions together with studies of other exercise protocols providing different and greater skeletal loading such as jogging and resistance training, but without including any subgroup analyses by exercise type. The more recent meta-analysis of walking-only interventions by Palombaro [14], reporting positive effects of walking interventions on BMD, also has several shortcomings including: contamination by interventions prescribing other exercise modes with walking [32], the inclusion of studies measuring other aspects of bone mineral [8], and including the same group of participants twice in the analysis [11,33].

We excluded interventions that combined walking with other weight-bearing exercise modalities from our review so as not to

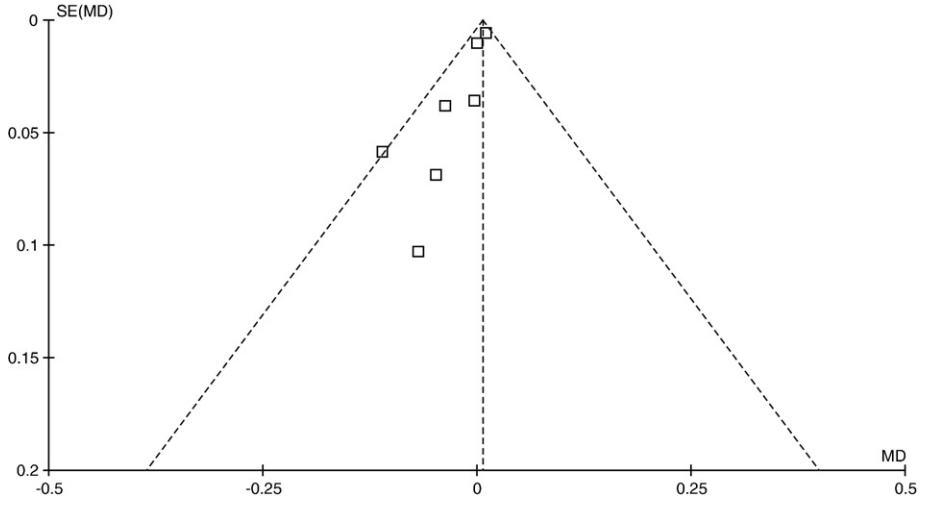

Fig. 4. Funnel plots for lumbar spine bone mineral density outcomes from RCTs including 95% CI lines. Vertical line represents zero effect size.

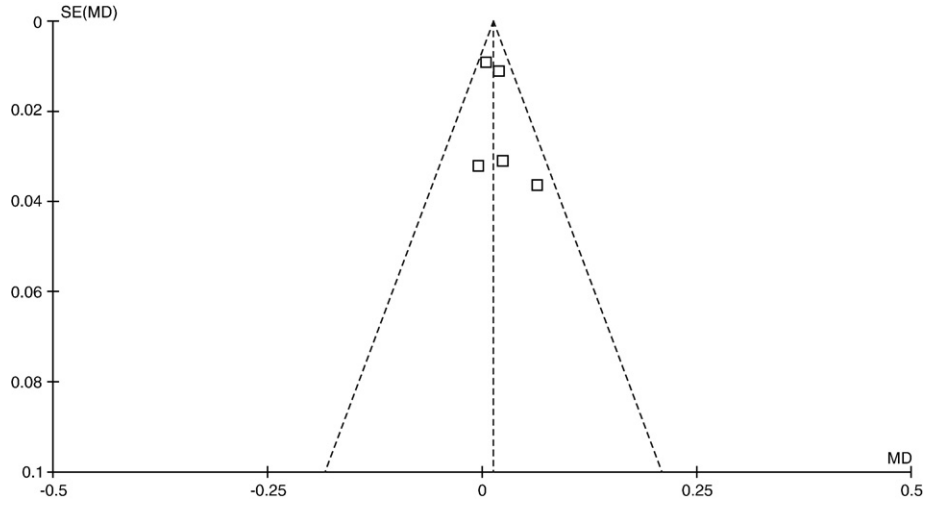

Fig. 5. Funnel plots for femoral neck bone mineral density outcomes from RCTs including 95% CI lines. Vertical line represents zero effect size.

contaminate effect estimates of walking with activities having differing and potentially greater loading characteristics, such as stepping or jogging [34]. Among these excluded trials [30–32,35–38] (meta-analysis not presented) the estimated treatment effect at lumbar spine was significant (0.013 g/cm^2; $P<0.0001$). It may be that the walking interventions prescribed in our included trials were not of sufficient frequency or duration to load the skeletal system over and above that of the everyday physical activity of the recruited participants. Indeed, one of the included RCTs [24] reported including a number of "very fit" participants. In the lumbar spine meta-analysis the effect estimate for this trial was negative.

The methodology employed by Bonaiuti et al. [13] is more sophisticated than that used by Bérard et al. [10] and Palombaro [14], and comparable to ours as we also carried out our review and meta-analysis in line with Cochrane Collaboration recommendations [15]. Although Bonaiuti et al. [13] observed significant effects of walking on BMD at both the hip and spine, the lower bound confidence intervals (CIs) for both sites were close to 0 (0.21 and −0.03). We observed negative lower bound CIs in our analyses of RCTs at these sites (−0.004 and −0.001), with non-significant BMD results. However, the trials we included were different to, and greater in number than those of Bonaiuti et al. [13]. Indeed their lumbar spine comparison of three RCTs included one where only the treatment arms were randomised [12], and only two trials were combined in their femoral neck comparison which we excluded as not non-walking-only interventions [30,31].

The relative changes we observed at both lumbar spine and femoral neck were also small. Within the meta-analysis of Wolff et al. [19], the included trials resulted in a 0.9% yearly increase in BMD following exercise versus 1% loss in controls. However, walking trials were combined with trials including other forms of weight-bearing activity. From the meta-analysis including just walking interventions, Palombaro [14] concludes that other forms of exercise should be incorporated with walking for patients at risk of osteoporosis.

In addition to our systematic review and meta-analysis we also assessed aspects of study quality of our included studies using a widely utilised instrument. We did not perform any analyses by trial quality score as aspects of design, blinding and attrition may have been more influenced by the level of reporting of these aspects in our included trials. However, we did perform analyses excluding trials with high attrition [24], with no substantive change in meta-analysis results. High attrition rates among studies of exercise and bone density is a recognised problem [39]. Notably, none of the included studies presented a valid intention-to-treat strategy where attrition occurred. Intention-to-treat analyses are preferred as they are unbiased in addressing clinically relevant research questions [20].

We planned subgroup analyses for potential effects of aspects of protocol design, including recruitment of participants already using HRT, nutritional co-interventions, and BMD scanning devices. We were only able to perform analyses for effects of differing BMD scanning devices used namely DPA and DXA. The trials included in our review represent a research era of some 15 years, with only the later trials using DXA, the gold standard for BMD assessment [40]. Treatment effects at both lumbar spine and femoral neck were similar for both devices and comparable with those of the overall meta-analyses results. Compliance with the walking programmes where reported was high among the trials included in our meta-analysis. No adverse effects associated with the exercise interventions were reported in any trial. However, there were a comparatively low number of fully supervised exercise trials, and some trials reported that most or all walking sessions were unsupervised [11,24].

Examination of funnel plots revealed symmetry of study effect sizes for femoral neck BMD outcomes whereas the lumbar spine plots appeared skewed towards trials with negative BMD outcomes. The lumbar spine has a higher proportion of trabecular bone than femoral neck [41], (with a potential for greater metabolic activity) and the interventions were of adequate duration for bone remodelling to occur [42]. It is possible that the loading forces of walking were neither not novel nor of sufficient magnitude to elicit an osseous effect over and above that of normal everyday activity of participants. A wider literature including animal studies [43,44] suggests that for mechanical loading to affect bone, it should be of sufficient magnitude and site-specific [45,46]. Additionally, there have been variable findings regarding mechanical loading effects on BMD between pre- and postmenopausal women [47,48]. Yamazaki et al. [28] found that whilst walking had an antiresorptive effect on bone in postmenopausal women, effects on lumbar spine BMD are only modest. A redistribution of bone mineral following exercise is also conceivable [49]. Indeed, one of our included trials observed a significant increase in calcaneal BMD [11]. Our negative lumbar spine findings may reflect such a systemic effect of walking on BMD, or a true effect reflective of the intensity of the intervention.

Limitations

The findings from our review and meta-analysis are limited by trials recruiting highly selected small samples of women where observed

effect sizes may be due to accidental selection of non-representative samples [50], along with inadequate reporting of treatment supervision and participant compliance. In addition, the trials were variable in study design, randomisation methods and treatment protocols. Trials of complex interventions such as exercise continue to present methodological challenges for meta-analysis.

Conclusions

The primary outcome for this review was BMD which is a surrogate marker for fractures [40]. There was a statistically significant effect of walking on femoral neck BMD but not lumbar spine, although the effect we observed at femoral neck is most likely too small to be of clinical significance in terms of fracture prevention [51]. However, a prospective cohort study has found that walking for at least 4 h/wk was associated with a 41% lower risk of hip fracture compared with walking for less than 1 h/wk [52]. Regular walking may be effective in reducing the risk of fracture by improving balance [53], and reducing risk for falling [54], beyond changes evident in BMD among postmenopausal women.

We conclude that walking as a singular exercise therapy has no significant effect on lumbar spine BMD in postmenopausal women. Whilst significant, positive effects at femoral neck are evident, diverse methodological and reporting discrepancies are apparent in published trials. Furthermore, the effects of walking on BMD may be too small clinically in relation to reduction of fractures. Interventions that combine walking with other forms of exercise that provide adequate skeletal loading and are more directly targeted at specific skeletal regions may be required. Current recommendations regarding walking for preserving bone mineral density in this population require revision.

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