

Effects of different impact exercise modalities on bone mineral density in premenopausal women: a meta-analysis

Marrissa Martyn-St James · Sean Carroll

Received: 4 August 2009 / Accepted: 9 October 2009 / Published online: 15 December 2009
© The Japanese Society for Bone and Mineral Research and Springer 2009

Abstract Our objective was to assess the effects of differing modes of impact exercise on bone density at the hip and spine in premenopausal women through systematic review and meta-analysis. Electronic databases, key journals and reference lists were searched for controlled trials investigating the effects of impact exercise interventions on lumbar spine (LS), femoral neck (FN) and total hip (TH) bone mineral density (BMD) in premenopausal women. Exercise protocols were categorised according to impact loading characteristics. Weighted mean difference (WMD) meta-analyses were undertaken. Heterogeneity amongst trials was assessed. Fixed and random effects models were applied. Inspection of funnel plot symmetry was performed. Trial quality assessment was also undertaken. Combined protocols integrating odd- or high-impact exercise with high-magnitude loading (resistance exercises), were effective in increasing BMD at both LS and FN [WMD (fixed effect) 0.009 g cm^{-2} 95% CI (0.002–0.015) and 0.007 g cm^{-2} 95% CI (0.001–0.013); $P = 0.011$ and 0.017 , respectively]. High-impact only protocols were effective on femoral neck BMD [WMD (fixed effect) 0.024 g cm^{-2} 95% CI (0.002–0.027); $P < 0.00001$]. Funnel plots showed some asymmetry for positive BMD outcomes. Insufficient numbers of protocols assessing TH BMD were available for assessment. Exercise programmes that combine odd- or high-impact activity with high-

magnitude resistance training appear effective in augmenting BMD in premenopausal women at the hip and spine. High-impact-alone protocols are effective only on hip BMD in this group. However, diverse methodological and reporting discrepancies are evident in published trials.

Keywords Bone density · Osteoporosis · Exercise · Systematic review · Meta-analysis

Introduction

Osteoporosis is a disease of bone that leads to an increased risk of fracture [1]. Physical activity has been suggested as an intervention strategy to promote optimal bone density during youth and to reduce the rate of bone loss during middle and later life [2, 3]. Bone tissue responds to dynamic as opposed to static loading, as static loads (even those that produce fairly large stresses or strains) do not initiate osteogenesis [4]. For physical activity to have an osteogenic effect, the mechanical loads applied to the skeleton need to be in excess of those encountered in daily activity [5]. Athletes involved in high-impact and odd-impact sports (such as hurdling, volleyball and squash) exhibit greater bone density than those involved in lower-impact sports (such as orienteering or skiing) [6].

Among postmenopausal women, we have recently demonstrated that the optimum impact exercise protocols for preservation of postmenopausal bone mass to be those that are odd- or high-impact in nature, combined with high magnitude resistance training [7]. Among non-athletic, premenopausal women, Bailey and Brooke-Wavell [8] suggest that high-impact activity may provide a useful method of assessing the relationship between loading and bone to help define the best exercise prescription for

M. Martyn-St James (✉)
Carnegie Faculty of Sport and Education, Leeds Metropolitan University, Room 202 Fairfax Hall, Headingley Campus, Leeds LS6 3QT, UK
e-mail: M.Martyn-St-James@leedsmet.ac.uk

S. Carroll
Leeds Metropolitan University, Leeds, UK

optimising peak bone mass premenopause. However, the optimum type of impact exercise programme for premenopausal women to best augment bone mass remains unquantified.

The purpose of the present study is to systematically review and meta-analyse the effects of differing impact exercise protocols on bone density in premenopausal women.

Methods

We conducted our systematic review and meta-analysis in line with Cochrane Collaboration recommendations [9] in conjunction with guidelines for quality of meta-analysis reporting [10]. The recommendations made by the Cochrane Musculoskeletal Group for improvements in systematic reviews of therapies for musculoskeletal conditions were also considered [11].

Search strategy

The following bibliographic databases were searched via Ovid to end December 2008: MEDLINE (1966), EMBASE (1980), PubMed (1966), Web of Science (1945), SportDiscus (1975), EBMZ (1917), and ProQuest (1995). Text words, key words and subject headings used in the searches included: women or females; running, exercise, physical therapy or physical activity; bone density, bone mineral density (BMD) or bone mass; osteoporosis or osteopenia; clinical trial, controlled trial or randomized controlled trial. Hand searching of key journals along with reference lists of other reviews [3, 12, 13], reference lists of articles identified for inclusion, and Web searches (<http://www.scholar.google.com>) were also undertaken. All citations were entered into reference management software (Reference Manager, version 11, Thomson ResearchSoft, Carlsbad, California).

Eligibility criteria

Trials reported as peer-reviewed articles, abstracts, theses and dissertations were eligible for inclusion, as were trials published in languages other than English. Only study groups comprising premenopausal women from controlled trials evaluating impact exercise interventions were included. Where multiple publications were by the same institution, group or author, clarity was sought regarding whether BMD data from the same study population had been reported in more than one article. Where trials reported BMD data for the same participants in more than one publication, data from only one of the articles were included to avoid double counting participants [14].

The interventions of interest were any exercise protocol that included any ground reaction force generating impact activity such as running or jumping-type movements where both feet leave contact with the ground. Treatment groups investigating the effects of impact activity combined with other forms of skeletal loading exercise such as resistance training were also included.

Outcomes

Outcomes for this review were defined as BMD (BMD g cm^{-2}) at the lumbar spine, femoral neck and total hip measured by radiographic techniques (SPA, single photon absorptiometry; DPA, dual photon absorptiometry; or DXA, dual X-ray absorptiometry) with standard deviations (SD).

Absolute change values in BMD from baseline to follow-up were used in the analyses. Where these values were not available from the original publication or author, these were calculated using baseline and follow-up values. Standard deviations for the change values were then imputed using a correlation coefficient value (r), calculated using baseline, follow-up and change values, from other included studies. The imputation method is detailed in the Cochrane Reviewers' Handbook [9].

Data extraction

Data were extracted from each article independently by two reviewers (MMSJ and SC). Details extracted included: participant characteristics, number 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 that had been prescribed to them as part of the intervention, region of interest (ROI) assessed and scanning technique, and BMD values with standard deviations (SD).

For trials including more than one exercise treatment group, the BMD outcome of the control group was used for each study group comparison within the meta-analysis, with the control group participant number divided amongst each of the comparisons. This process ensures that control participants are not counted more than once within the meta-analysis [14].

An assessment of trial quality was undertaken for comparative purposes using the questionnaire described by Jadad et al. [15]. This is a three-item instrument that provides an assessment of bias, specifically randomization, 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.

Meta analysis

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 [16]. WMDs were calculated using fixed-effect and random-effects models.

We undertook the following a priori subgroup analyses to investigate the differing skeletal loading characteristics of the protocols [6, 17]: (1) high-impact loading, such as vertical jumps or rope jumping, or running at $>9 \text{ km h}^{-2}$; (2) odd-impact loading, such as aerobic or step classes, bounding exercises, agility exercises and games where movements included directional elements to which the body is not normally accustomed; (3) low-impact loading such as jogging at $<9 \text{ km h}^{-2}$; and (4) combined loading protocols of impact activity mixed with high-magnitude joint reaction force loading through resistance training. Sensitivity analyses were also undertaken to assess aspects of trial design, specifically randomisation.

Assessment of heterogeneity

Heterogeneity of net study group changes in BMD was examined using the Q statistic. A P value of < 0.10 was adopted since the Q statistic tends to suffer from low differential power [18]. Consistency of treatment effects across trials was assessed using the I^2 statistic, with I^2 values of $\leq 50\%$ considered to reflect low heterogeneity, those with 50–75% considered moderate, and I^2 values of $\geq 75\%$ considered highly heterogeneous [18]. Together with this interpretation of I^2 values, 95% confidence intervals (CI) were calculated for each I^2 value [19].

Tests for overall effect (Z score) were considered significant at $P < 0.05$.

Publication bias

Publication bias was examined through funnel plot inspection [14]. 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, although publication bias is not the only possible cause of asymmetry [20].

Meta-analysis and production of all graphics was performed using STATA version 10 (StataCorp, TX, USA).

Results

From the searches, 42 exercise intervention studies among premenopausal women were identified for potential inclusion and full text versions obtained (Fig. 1). Of these, 25 studies did not evaluate impact exercise interventions and were excluded. Seventeen of the trials evaluated impact exercise interventions. Eight of these did not meet all inclusion criteria for this review and were excluded. Reasons for exclusion are given in Fig. 1 (details of all excluded studies are available from the authors). Nine trials comparing impact exercise with a non-exercise control group and reporting BMD outcomes assessed by radiographic techniques at the hip and/or spine in premenopausal women were included [21–29]. Study group allocation was reported as randomised in six of the included trials [21–27]. Details of study design, participant details, exercise protocols, BMD outcomes and trial quality assessment are presented in Table 1.

Participant characteristics

With the exception of one study recruiting both Asian and Caucasian women [22], all studies recruited Caucasian women. Two studies recruited participants in the third decade [24, 27], one from the fourth [26] and one the fifth [25]. Four studies recruited participants from the fourth and fifth decade [21, 23, 28, 29] and one from the third and fourth decade [22].

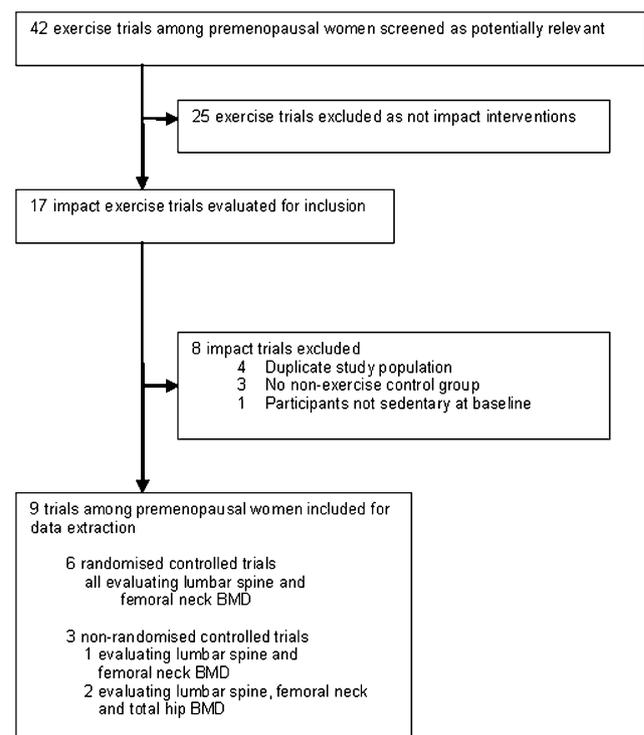


Fig. 1 Study selection process

Table 1 Details of controlled trials of impact training effects on BMD among premenopausal women

Study, country, design and participants including OC use	Age range/ mean \pm SD, years	Exercise protocol, frequency, intensity, progression, supervision, duration, additional supplementation plus impact category	Participant numbers	Protocol compliance (%)	BMD outcomes and change scores
Bassey et al. [22] UK Randomised controlled trial Women in good health and able to exercise. Premenopausal women with BMD more than 2.00 SD below young adult excluded. No statement on OC use	Treatment: 38.4 \pm 7.4 Control: 36.4 \pm 7.6	50 jumps—5 sets of 10 Frequency: 6 days/week Intensity: 1,993 \pm 97 N; 301 \pm 11% body weight Progression: no statement Duration: 12 months Supervision: One session per week Impact category: high impact	Treatment: Completed—30 Controls: Completed—35 Overall: Total—88 Withdrawn—33	91	BMD at lumbar spine L2–L4 and femoral neck assessed by DXA (Lunar DPX-L) Change scores reported in article, SDs estimated from reported SEs
<i>Quality assessment score:</i> study described as randomised—1, described as double blind—0, description of withdrawals—1, total—2					
Friedlander et al. [23] US Randomised controlled trial Caucasian and Asian women. Excluded medical conditions known to affect BMD, use of oral contraceptives, Ca intake >300 or <1,000 mg, history of current participation in vigorous physical activity or BMD more than 2.00 SD below young adult. No statement on OC use	Range: 20–35 Treatment: 28.0 \pm 6.8 Control: 30.1 \pm 4.0	Three different 1 h exercise classes. Class 1: circuit class of high-impact and weight stations (push ups, sit ups, arm curls). Class 2: group exercise resistance training only, inc upper body and lower—glutes, quads back and shoulders, using dumbbells and barbells. Class 3: vigorous high-impact aerobics. Frequency: 3 days/week (1 of each class type) Intensity: 3, 6, 12 lb dumbbells; 16–36 lb barbells; aerobics 70–85% HRmax Progression: increase in weights used over 24 months Duration: 24 months Supervision: all sessions supervised Some exercise ($n = 17$) and control ($n = 14$) given 1,500 mg/day Impact category: combined (odd/high-impact with resistance training)	Treatment: Completed—32 Controls: Completed—31 Overall: Total—127 Withdrawn—64	61.3	BMD at lumbar spine and femoral neck assessed by DXA (Hologic QDR 1,000) Change scores with SDs estimated from relative change scores reported in article.
<i>Quality assessment score:</i> study described as randomised—2, described as double blind—0, description of withdrawals—1, total—3					

Table 1 continued

Study, country, design and participants including OC use	Age range/ mean \pm SD, years	Exercise protocol, frequency, intensity, progression, supervision, duration, additional supplementation plus impact category	Participant numbers	Protocol compliance (%)	BMD outcomes and change scores
Heinonen et al. [24] Finland Randomised controlled trial Premenopausal women. Excluded physical and medical restrictions to training and conditions affecting BMD inc smoking, alcohol, PA, BMI. No statement on OC use	Range: 35–45 Treatment: 39 \pm 3 Control: 39 \pm 3	Sessions including 15 min warm-up, 20 min jumping or stepping exercises, 15 min callisthenics, 10 min cooldown Frequency: 3 days/week Intensity: peak force between 2.1 and 5.6 \times body weight Progression: jumping hurdles and step height increased Duration: 18 months Supervision: all sessions supervised Impact category: odd-impact	Treatment: Total—49 Completed—39 Withdraw—10 Controls: Total—49 Completed—45 Withdraw—4	83	BMD at lumbar spine L2–L4 and femoral neck assessed by DXA (Norland XR-26) Change scores with SDs estimated from graphs reported in article
<i>Quality assessment score:</i> study described as randomised—1, described as double blind—0, description of withdrawals—1, total—2					
Kato et al. [25] Japan Randomised controlled trial Female college students. No statement on OC use	Treatment: 20.5 \pm 0.6 Control: 20.9 \pm 0.8	Ten two-legged vertical jumps with arm swings performed bare foot Frequency: 3 days/week Intensity: peak GRF takeoff 2.35 landing 4.76 \times body weight Progression: no statement Duration: 6 months Supervision: unsupervised 17 jumping and 17 control group participants given 300 mg/day Ca Impact category: high-impact alone	Treatment: Total—18 Completed—18 Withdraw—0 Controls: Total—18 Completed—18 Withdraw—0 42 recruited overall, 6 excluded from analysis due to poor compliance	82	BMD at lumbar spine L2–L4 and femoral neck assessed by DXA (Aloka) Change scores with SDs provided
<i>Quality assessment score:</i> study described as randomised—1, described as double blind—0, description of withdrawals—1, total—2					

Table 1 continued

Study, country, design and participants including OC use	Age range/ mean \pm SD, years	Exercise protocol, frequency, intensity, progression, supervision, duration, additional supplementation plus impact category	Participant numbers	Protocol compliance (%)	BMD outcomes and change scores
Sugiyama, Yamaguchi and Kawai [26] Japan Controlled trial					
Premenopausal Japanese women around 50 years old with regular menstruation cycle. Smoking and alcohol consumption excluded No statement on OC use	Treatment: 48 \pm 1 Control: 47 \pm 1	Rope skipping 100 jumps a day Frequency: 2–3 days/week Intensity: no statement Progression: no statement Duration: 6 months Supervision: no statement Impact category: high-impact alone	Treatment: Total—not reported Completed—14 Withdraw—not reported Controls: Total—not reported Completed—16 Withdraw—not reported	Excluded if did not meet 50	BMD at lumbar spine L2–L4, femoral neck and total hip assessed by DXA (Hologic QDR 4500) Change scores with SDs provided
<i>Quality assessment score:</i> study described as randomised—0, described as double blind—0, description of withdrawals—0, total—0					
Vainionpää et al. [27] Finland Randomised controlled trial					
Premenopausal women free from cardiovascular, musculoskeletal, respiratory or other diseases or medication affecting bone. Regular participation in high-impact activity more than three times a week excluded. No statement on OC use	Treatment: 38.1 \pm 1.7 Control: 38.5 \pm 1.6	Exercise classes inc 40 min high-impact activity: step patterns, stamping, jumping, running and walking. Step benches introduced at 3 months to enhance impact effects Frequency: 3 days/week Intensity: no statement Progression: by adding bench step Duration: 12 months Supervision: all sessions supervised Impact category: odd-impact alone	Treatment: Total—60 Completed—39 Withdraw—21 Controls: Total—60 Completed—41 Withdraw—19	Average attendance 0.9 days/week	BMD at lumbar spine L1–L4 and femoral neck assessed by DXA (Hologic Delphi QDR) Change scores with SDs provided
<i>Quality assessment score:</i> study described as randomised—2, described as double blind—0, description of withdrawals—1, total—3					

Table 1 continued

Study, country, design and participants including OC use	Age range/ mean \pm SD, years	Exercise protocol, frequency, intensity, progression, supervision, duration, additional supplementation plus impact category	Participant numbers	Protocol compliance (%)	BMD outcomes and change scores
Weaver et al. [28] US Randomised controlled trial Minimally active young women free from meds and disorders affecting Ca metabolism, no less than 9 menses during past 12 months, not pregnant or lactating in past 3 months. OC users and non-users recruited	Treatment (OC): 24.1 \pm 3.5 Control (OC): 24.2 \pm 3.7 Treatment (non OC): 23.9 \pm 4.0 Control (non OC): 24.1 \pm 3.9	60 min skipping per week plus 2 sets, 8-12 reps, of 8 upper body and 8 lower body resistance training stations (Universal circuit room) Frequency: 3 days/week Intensity: GRF 1.9 \times body weight JRF 3.14 BW Progression: no statement Duration: 6 months Supervision: unsupervised Impact category: combined (odd/high-impact with resistance training)	Treatment: (OC) Total—19 Completed—19 Withdraw—0 Controls (OC): Total—19 Completed—19 Withdraw—0 Treatment: (non OC) Total—37 Completed—26 Withdraw—11 Controls (non OC): Total—24 Completed—20 Withdraw—4	43.7 skipping 46.7 strength	BMD at lumbar spine L2–L4 and femoral neck assessed by DXA (Lunar) Change scores with SDs provided

Quality assessment score: study described as randomised—1, described as double blind—0, description of withdrawals—1, total—2

Table 1 continued

Study, country, design and participants including OC use	Age range/ mean \pm SD, years	Exercise protocol, frequency, intensity, progression, supervision, duration, additional supplementation plus impact category	Participant numbers	Protocol compliance (%)	BMD outcomes and change scores
Winters-Stone and Snow [29]					
US					
Controlled trial					
Premenopausal women (9–12 menstrual cycles in the previous 12 months). Excluded history of chronic disease, smoking, breast feeding, intention to become pregnant within the next year, regular participation in resistance training or high-impact exercise. Women engaged in aerobic activities, such as walking or jogging, were not excluded.	Treatment 1: 38.3 \pm 3.8 Treatment 1: 41.3 \pm 3.8 Control: 40.5 \pm 3.5	Group 1: lower body only—9 sets of 10–12 jumps (off the ground, side to side and off wooden boxes), single and double leg stance, and 9 sets of 10–12 repetitions of lower body resistance exercises using weighted vests. Group 2: lower and upper body—9 sets of 10–12 jumps (off the ground, side to side and off wooden boxes), single and double leg stance, and 9 sets of 10–12 repetitions of lower body resistance exercises using weighted vests plus three sets of 8–12 repetitions of 8 upper body exercises, using bands. One type of exercise for each major muscle group was performed at each session. Frequency: 3 days/week (exercises for one upper body major muscle group performed at each session) Intensity: bands 8–12RM Progression: increased by increasing weighted vest Duration: 12 months Supervision: all sessions supervised Impact category: combined (odd/high-impact with resistance training)	Treatment 1: Total—21 Completed—19 Withdraw—2 Treatment 2: Total—21 Completed—16 Withdraw—5 Controls: Total—24 Completed—24 Withdraw—0	71	BMD at lumbar spine L2–L4, femoral neck and total hip assessed by DXA (Hologic QDR 1000). Change scores not reported. Follow-up values with SDs reported in article
No statement on OC use					
<i>Quality assessment score:</i> study described as randomised—0, described as double blind—0, description of withdrawals—1, total—1					

Table 1 continued

Study, country, design and participants including OC use	Age range/ mean \pm SD, years	Exercise protocol, frequency, intensity, progression, supervision, duration, additional supplementation plus impact category	Participant numbers	Protocol compliance (%)	BMD outcomes and change scores
Winters, Titus and Snow [30] US Controlled trial					
Premenopausal women 35–45, excluded if disease known to affect BMD, > 40% body fat, smoking, breast feeding, irregular menses, high intensity resistance or high-impact training. No statement on OC use	Treatment: 39.6 \pm 4.2 Control: 40.5 \pm 3.3	Wearing weighted vests—nine sets of 10–12 jumps performed directionally and using 12in boxes; and nine sets of 10–12 reps lower body resistance exercises—squats, side lunges, back lunges, forward lunges. Frequency: 3 days/week Intensity: no statement Progression: increased by increasing weighted vest Duration: 12 months Supervision: no statement Impact category: combined (odd/high-impact with resistance training)	Treatment: Total—41 Completed—29 Withdrawn—12 Controls: Total—24 Completed—20 Withdrawn—4	No statement	BMD at lumbar spine L2–L4 and femoral neck assessed by DXA (Hologic QDR 1000) Change scores not reported. Follow-up values with SDs reported in article

Quality assessment score: study described as randomised—0, described as double blind—0, description of withdrawals—1, total – 1

BMD bone mineral density, *Ca* calcium, *N* Newtons, *HR*_{max} maximum heart rate, *GRF* ground reaction force, *JRF* joint reaction force, *BW* body weight, *RM* repetition maximum, *OC* oral contraception, *DPA* dual photon absorptiometry, *DXA* dual X-ray absorptiometry, *SD* standard deviation, *SE* standard error

Exercise protocols

Three studies prescribed high-impact loading exercise where vertical jumping or skipping was the singular mode of exercise [21, 24, 25]. Two studies evaluated group exercise interventions providing odd-impact loading forces such as stamping, bench stepping and hurdle bounding [23, 26]. Four studies evaluated combined loading protocols as either circuit type or other group exercise where odd-impact and/or high-impact exercises were combined with resistance training and/or weighted vest work [22, 27–29]. With the exception of one study prescribing training frequency of 6 days a week [21], training frequency of interventions was 2–3 times weekly. Progression of impact loading during the time course of the intervention was reported in four studies [23, 26, 28, 29].

Study duration was 6 months in two studies [25, 27] and 12 months in four studies [21, 26, 28, 29]. One study was 18 months in duration [23] whilst another reported final follow-up at 24 months [22].

Adjuvant supplementation

One study increased daily calcium intake levels of all participants with low dietary calcium intake by means of supplementation during the intervention [24].

Pharmacotherapy use

One study was factorially designed to assess oral contraception (OC) effects on BMD combined with exercise, allocating participants to four study groups: two exercise

groups, one of OC users and one of non-users, plus two non-exercise control groups, again one of OC users and one of non-users [27].

Supervision and compliance

Supervision was reported on in six studies [21–24, 27, 28]. All sessions were supervised in five of these [22–24, 27, 28], but only 1 day a week was supervised in one [21]. Exercise compliance as a percentage of sessions attended was reported on in six studies [21–24, 27, 29], where it ranged from approximately 45% [27] to 91% [21].

BMD outcomes

BMD at lumbar spine and femoral neck was assessed in all nine studies. Total hip BMD was assessed in only two studies [25, 28] and therefore no meta-analysis was undertaken for the effects of impact training for this ROI. All nine studies assessed BMD using DXA equipment.

Absolute change values in BMD at follow-up along with SDs were available for five studies [21, 24–27]. Values were estimated from reported relative change values for one study [22], and from graphical presentation of change scores in another [23]. Absolute change values in BMD at follow-up were estimated for two studies [28, 29], with the associated SD imputed from the correlation coefficient of studies reporting both change and follow-up scores ($r = 0.99$). Absolute final values in BMD at follow-up with SDs were available for seven studies [21, 24–29].

Fig. 2 Forest plot showing effects of impact exercise training at the lumbar spine in premenopausal women. *WMD* weighted mean difference (g/cm^2), *I-V* inverse variance (fixed-effect), *D + L* DerSimonian and Laird (random-effects), *dotted line* line of mean treatment effect, *diamond* overall treatment effect with 95% CI

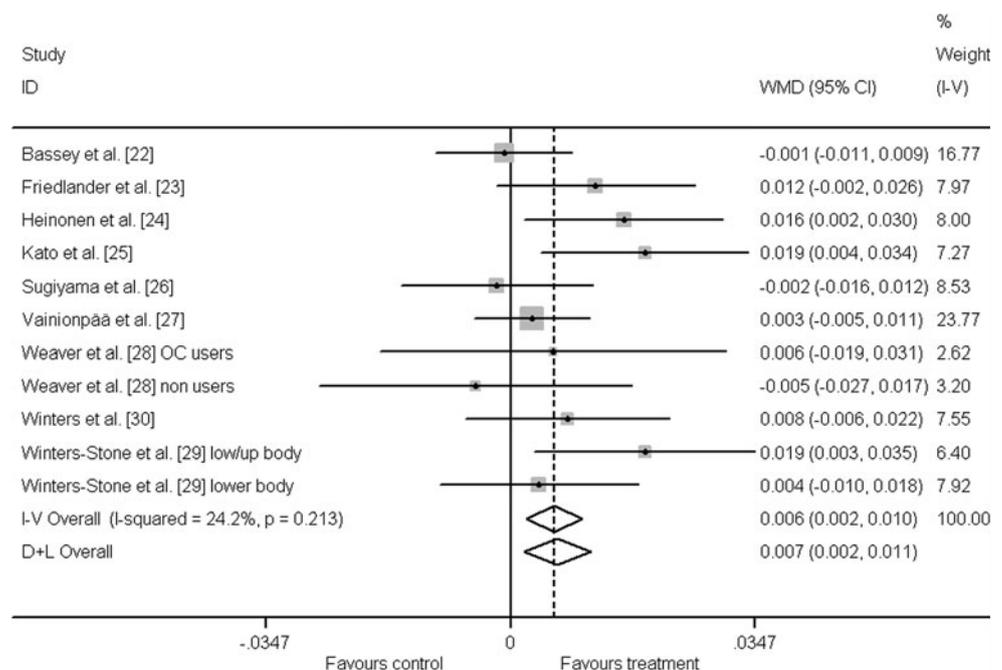
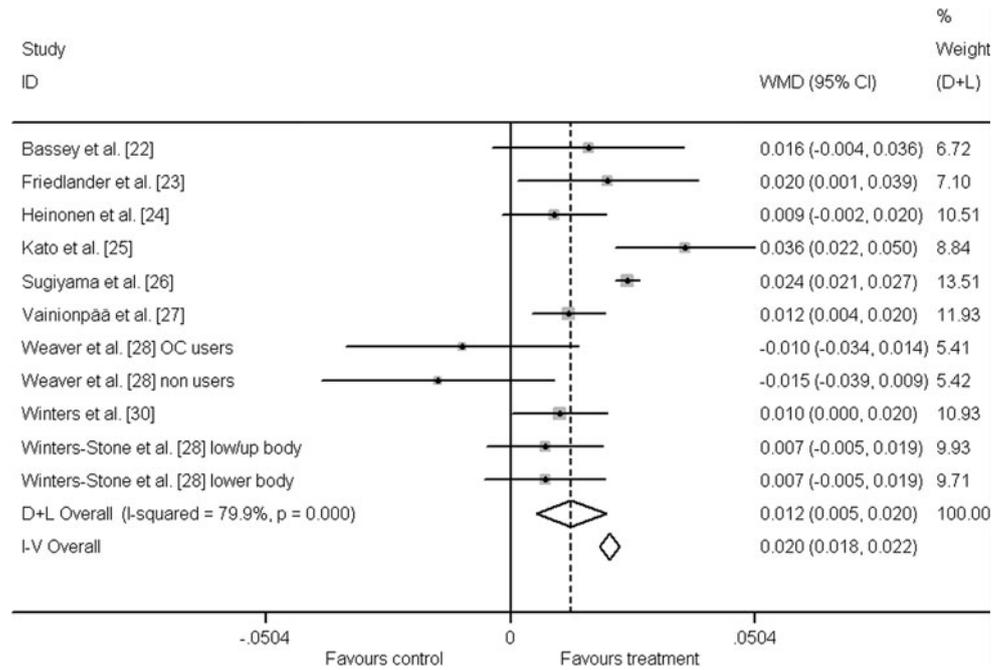


Fig. 3 Forest plot showing effects of impact exercise training at the femoral neck in premenopausal women. *WMD* weighted mean difference (g/cm^2), *I-V* inverse variance (fixed-effect), *D + L* DerSimonian and Laird (random-effects), *dotted line* line of mean treatment effect, *diamond* overall treatment effect with 95% CI



Loss to follow-up

Loss to follow-up (participants assigned versus those completing end-point assessment) was reported in all but one of the studies [24]. Attrition $\geq 30\%$ was reported in one study with 50% of all study participants withdrawing [22].

Quality assessment score

The quality assessment instrument scores awarded to studies ranged from 0 to 3. All of the RCTs were awarded one point for randomisation with two studies being allocated one extra point available for describing the randomisation process [22, 26]. All studies, with the exception of one [24], were awarded one point for statements regarding withdrawal of participants. No study gained points for blinding of participants or contained a description of adequate concealment of allocation. One study was awarded no points at all [24].

Meta-analysis

All of the included trials assessed lumbar spine BMD and provided 11 study group comparisons of impact exercise interventions versus control. A total of 281 participants were assigned to exercise and 240 to non-exercise control. Low heterogeneity was observed in the initial meta-analysis including all study group comparisons ($I^2 = 24$, 95% CI: 0.0–62%). A significant effect of impact exercise interventions on BMD at this site was evident ($P = 0.003$).

The combined WMD in BMD was 0.006 g cm^{-2} [WMD (fixed effect) 95% confidence interval (CI), 0.002–0.010].

In contrast the meta-analysis including the same study group comparisons for femoral neck was highly heterogeneous ($I^2 = 80\%$, 95% CI: 65–89%). The combined WMD in BMD at femoral neck was 0.012 g cm^{-2} [WMD (random effects) 95% confidence interval (CI), 0.005 to 0.020; $P = 0.001$].

Figures 2 to 3 show the results from meta-analysis of all included trials. Table 2 lists results from all sensitivity and subgroup analyses.

Sensitivity analysis including only trials of random design (RCTs) assessing lumbar spine BMD [21–24, 26, 27] did not show any great divergence from the low heterogeneity evident in the overall analysis for this site [I^2 value was 34% (95% CI: 0.0–72.1%)]. Amongst the RCT study groups the WMD in BMD at this site was 0.006 g cm^{-2} [(fixed effect) 95% confidence interval (CI), 0.001–0.011]. Again, the effect of impact exercise at this site was significant ($P = 0.01$). At the femoral neck, moderate to high heterogeneity was observed amongst the same RCT study groups ($I^2 = 68\%$, 95% CI: 33.6–86.2%). The WMD in BMD amongst RCT study groups at this site was 0.012 g cm^{-2} [(random effects) 95% confidence interval (CI), 0.001 to 0.022; $P = 0.03$].

The subgroup analysis of trials evaluating protocols of high-impact exercise alone showed heterogeneity ($I^2 = 65\%$, 95% CI: 0.0–89.9%) with no positive effects evident at the lumbar spine (Table 2). In contrast, lower heterogeneity was observed in the femoral neck analysis

Table 2 Impact training meta-analysis results in premenopausal women by region of interest

Analysis	Lumbar spine		Femoral neck		Total hip	
	Fixed-effect	Random-effects	Fixed-effect	Random-effects	Fixed-effect	Random-effects
All included studies—change scores						
No. study group comparisons	11		11			N/A
No. participants						
Exercise	281		281			
Control	240		240			
Heterogeneity (<i>P</i> value)	0.21		(<0.00001)			
Inconsistency (<i>I</i> ² value)	24.2% (0.0–62.3%)		79.9% (64.9–88.5%)			
WMD (g cm ⁻²) 95% confidence interval	0.006 (0.002–0.010)	0.007 (0.002–0.011)	0.020 (0.018–0.022)	0.012 (0.005–0.020)		
Test for overall effect (<i>Z</i> score and <i>P</i> value)	3.02 (0.003)	2.75 (0.006)	18.79 (<0.00001)	3.39 (0.001)		
All RCTs						
No. study group comparisons	7		7			N/A
No. participants						
Exercise	203		203			
Control	180		180			
Heterogeneity (<i>P</i> value)	0.17		0.003			
Inconsistency (<i>I</i> ² value)	34.0% (0.0–72.1%)		69.7% (33.6–86.2%)			
WMD (g cm ⁻²) 95% confidence interval	0.006 (0.001–0.011)	0.007 (0.001–0.013)	0.013 (0.008–0.018)	0.012 (0.001–0.022)		
Test for overall effect (<i>Z</i> score and <i>P</i> value)	2.46 (0.014)	2.14 (0.033)	5.00 (<0.00001)	2.23 (0.026)		
High-impact only protocols						
No. study group comparisons	3		3			N/A
No. participants						
Exercise	62		62			
Control	59		59			
Heterogeneity (<i>P</i> value)	0.06		0.195			
Inconsistency (<i>I</i> ² value)	64.9% (0.0–89.9%)		38.8% (0.0–81.0%)			
WMD (g cm ⁻²) 95% confidence interval	0.003 (–0.004–0.010)	0.005 (–0.008–0.017)	0.024 (0.022–0.027)	0.025 (0.018–0.033)		
Test for overall effect (<i>Z</i> score and <i>P</i> value)	0.90 (0.367)	0.73 (0.463)	19.34 (<0.00001)	6.31 (<0.00001)		
Combined impact/resistance protocols						
No. study group comparisons	6		6			N/A
No. participants						
Exercise	141		141			
Control	95		96			
Heterogeneity (<i>P</i> value)	0.58		0.193			
Inconsistency (<i>I</i> ² value)	0% (0.0–66.6%)		32.3% (0.0–72.7%)			

Table 2 continued

Analysis	Lumbar spine		Femoral neck		Total hip	
	Fixed-effect	Random-effects	Fixed-effect	Random-effects	Fixed-effect	Random-effects
WMD (g cm ⁻²) 95% confidence interval	0.009 (0.002–0.015)	0.009 (0.002–0.015)	0.007 (0.001–0.013)	0.006 (–0.001–0.014)		
Test for overall effect (Z score and P value)	2.55 (0.011)	2.55 (0.011)	2.39 (0.017)	1.65 (0.100)		
All combined (impact with resistance) studies ≥10 months duration						
No. study group comparisons	4		4			N/A
No. participants						
Exercise	96		96			
Control	75		75			
Heterogeneity (P value)	0.553		0.672			
Inconsistency (I ² value)	0% (0.0–78.1%)		0% (0.0–70.3%)			
WMD (g cm ⁻²) 95% confidence interval	0.010 (0.003–0.018)	0.010 (0.003–0.018)	0.010 (0.003–0.016)	0.010 (0.003–0.016)		
Test for overall effect (Z score and P value)	2.79 (0.005)	2.79 (0.005)	3.06 (0.002)	3.06 (0.002)		
All combined (impact with resistance) studies with attrition ≤30%						
No. study group comparisons	5		5			N/A
No. participants						
Exercise	104		104			
Control	64		64			
Heterogeneity (P value)	0.47		0.254			
Inconsistency (I ² value)	0% (0.0–76.4%)		25.1% (0.0–69.8%)			
WMD (g cm ⁻²) 95% confidence interval	0.008 (0.000–0.015)	0.008 (0.000–0.015)	0.006 (0.000–0.012)	0.005 (–0.003–0.012)		
Test for overall effect (Z score and P value)	2.00 (0.046)	2.00 (0.046)	1.83 (0.067)	1.25 (0.210)		

for this type of exercise ($I^2 = 39\%$, 95% CI: 0.0–81.0%). The observed effect of this type of exercise on BMD at this site was significant ($P < 0.00001$).

Too few study group comparisons were available for high-impact-exercise-alone protocols to assess the effects of study duration or attrition on either lumbar spine or femoral neck BMD.

Subgroup analyses for the effects of combined loading protocols that integrated odd- or high-impact activity with high-intensity resistance exercises were homogeneous in having a positive effect at the lumbar spine ($I^2 = 0\%$, 95% CI: 0.0–66.6%). An increase in BMD of 0.009 g cm^{-2} [(fixed effect) 95% confidence interval (CI), 0.002 to 0.015; $P = 0.01$] was observed at this site. A significant positive effect on femoral neck BMD was also observed following this type of exercise programme ($I^2 = 32\%$, 95% CI: 0.0–72.7%; WMD 0.007 g/cm^2 [(fixed effect) 95% confidence interval (CI), 0.001 to 0.013; $P = 0.02$]).

Only two studies assessing lumbar spine and femoral neck BMD evaluated odd-impact protocol effects [23, 26], therefore analysis for this comparison was not undertaken.

Subgroup analyses including combined loading protocol trials of duration ≥ 10 months duration also displayed low heterogeneity for both lumbar spine ($I^2 = 0\%$, 95% CI: 0.0–78.1%) and femoral neck ($I^2 = 0\%$, 95% CI: 0.0–70.3%). Again, significant positive effects were evident at both sites (WMD 0.010 g/cm^2 [(fixed effect)]; $P = 0.005$ and 0.05 , respectively). Sensitivity analyses including only study group comparisons from combined loading protocol trials with attrition of $\leq 30\%$ also displayed low heterogeneity at both sites ($I^2 = 0\%$, 95% CI: 0.0–76.4% and $I^2 = 25.1\%$, 95% CI: 0.0–69.8%, respectively). Positive effects were evident and significant at lumbar spine (WMD 0.008 g/cm^2 [(fixed effect) 95% confidence interval (CI), 0.001 to 0.015; $P = 0.05$]).

Funnel plots were produced for the effects of impact exercise interventions on lumbar spine BMD (Fig. 4) and femoral BMD (Fig. 5), from all included trials. Visual inspection of these plots indicated some degree of asymmetry of trials showing a positive treatment effect at both sites. The femoral neck plot included a number of outliers appearing to have significant effect sizes in both positive and negative directions, with few studies in the central core, resulting in a tunnel effect.

Discussion

The primary purpose of this study was to undertake a systematic review and meta-analysis of trials assessing the effects of different modes of impact exercise on BMD at the hip and spine in premenopausal women. The second purpose was to help provide more information on differing

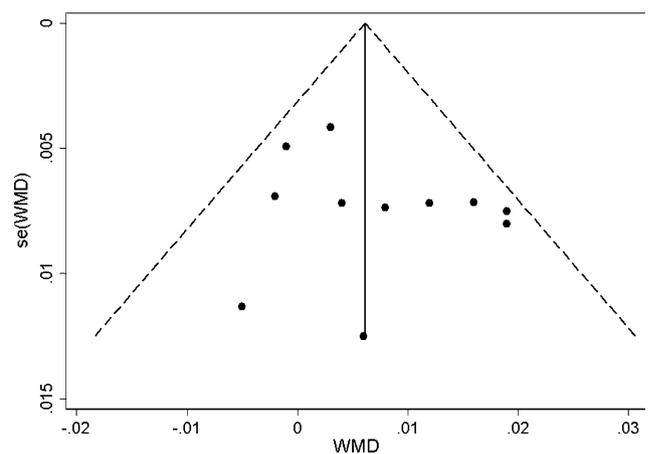


Fig. 4 Funnel plot for lumbar spine BMD outcomes (change scores) in premenopausal women, all included studies. *SE (WMD)* standard error of weighted mean; *WMD* weighted mean difference (fixed effect), *dotted lines* pseudo 95% confidence intervals

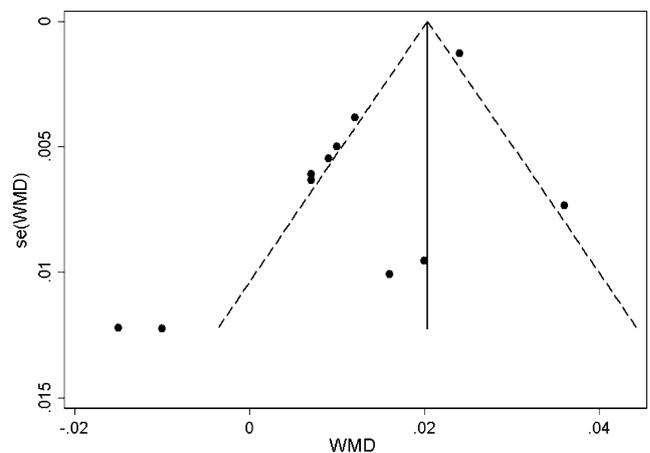


Fig. 5 Funnel plot for femoral neck BMD outcomes (change scores) in premenopausal women, all included studies. *SE (WMD)* standard error of weighted mean; *WMD* weighted mean difference (fixed effect), *dotted lines* pseudo 95% confidence intervals

types of impact exercise protocols for the purpose of prescribing optimal bone loading exercise regimes for premenopausal women.

Our findings indicate that structured exercise programmes that combine odd- or high-impact loading with high-magnitude loading (resistance training) are effective at significantly improving BMD at the lumbar spine and femoral neck in premenopausal women, whereas the effect of protocols that include high-impact exercise alone appear to be limited to increases in femoral neck BMD, but not the lumbar spine.

We included both randomised and non-randomised trials reported in peer-reviewed journals, theses, dissertations or abstracts. Our analyses including only RCT data yielded similar effect estimates compared with the included trials

that employed non-random allocation methods (meta-analysis not presented). These findings are inconsistent with Altman et al. [30], and with other meta-analyses of exercise effects on bone in both pre- and postmenopausal women [7, 13, 31]. Trials with inadequate allocation concealment tend to exaggerate estimates of intervention effects, compared with those with adequate concealment [32]. However, a recent meta-epidemiological study of 146 meta-analyses, including 1346 trials examining a wide range of interventions and outcomes, reported that mean bias associated with lack of adequate allocation concealment was less for trials with objectively assessed outcomes than those with subjectively assessed ones [33].

In the present study, the analyses combining all included impact exercise trials produced positive effect estimates of BMD change at both lumbar spine and femoral neck. Restricting these analyses to only RCT study groups resulted in similar effect sizes. Preventing selection and confounding biases are generally regarded as the most important advantage of randomisation [34]. It is notable that the compliance with the exercise protocols of our included studies was high whether they were randomised or not, and attrition was generally low, which may have contributed to the comparable positive findings between the overall analyses and sensitivity analyses of RCTs only.

To our knowledge, the present study is the first systematic review to include a meta-analysis that attempts to not only assess the effects of impact exercise on BMD outcomes in premenopausal women, but also to identify the optimum impact exercise programme to best preserve BMD in this population. Our overall analyses including all impact exercise studies and the sensitivity analyses including RCTs only produced more conservative effect estimates at both lumbar spine and femoral neck compared with the subgroup analyses of exercise protocols combining odd- or high-impact exercise with resistance training. Similar observations were evident at femoral neck when compared with the subgroup analysis of the high-impact only protocols.

In a review of factors interacting with physical activity effects on bone, Borer [35] asks whether principles shown to produce increments in bone mass using animal models have been appropriately applied to human studies. Namely, that adaptive bone response requires dynamic rather than static mechanical stimulation, adaptive bone response requires supra-threshold intensity, osteogenic response is proportional to strain frequency, adaptive bone response is improved with brief but intermittent exercise and, adaptive bone responses require an unusual pattern of bone loading. The largest effect sizes we observed at both lumbar spine and femoral neck were from protocols where odd and high-impact loading was combined with high-magnitude loading (high-intensity resistance training) [22, 27–29], whilst

high-impact-only protocols were highly effective only at the femoral neck [21, 24, 25]. This would suggest that these exercise formats, including their specific ground reaction force elements, provide a loading stimulus that is both adequate in its intensity and novel in its loading pattern at these sites. However, because of the differing combinations of skeletal loading activities evaluated in the trials included in these analyses, it is unreasonable to recommend exercise programmes based on only the impact components of these regimes alone (odd-impact, high-impact). The ground reaction forces of the high-impact-only protocols may not have been of great enough magnitude and may have been dissipated at the spine [36, 37]. The three high-impact [21, 24, 25] studies, all of which prescribed jumping or skipping, were all effective on femoral neck BMD despite variations in the number of jumps per day and the frequency of sessions per week, which ranged from two or three [24, 25] to 6 days per week [21]. This is in agreement with observations from animal studies that suggest high-impact loading either once, daily or a few times a week can have a positive effect on bone mass and strength [38].

A redistribution of bone mineral to the hip following high-impact only exercise is also conceivable [39].

In addition to our systematic review and meta-analysis we also assessed aspects of trial quality of our included trials using a widely utilised instrument [15]. However, points for blinding awarded by the instrument were redundant for all trials—reflecting a limitation of this instrument when assessing quality of exercise interventions. We did not perform any analyses by trial quality score as aspects of trial design, blinding and attrition may have been influenced more by the level of reporting of these aspects in our included trials. Approximately half of our included trials were published prior to the CONSORT (Consolidated Standards of Reporting Trials) statement [40]. Examination of funnel plots revealed some asymmetry of positive effect sizes for both lumbar spine and femoral neck BMD outcomes. However, the small number of study group comparisons available for funnel plot interpretation may not have been sufficient to distinguish real asymmetry [41]. The funnel plot for femoral neck outcomes displayed an interesting feature of a “tunnel effect” [42]. This has been cited as being indicative of a possible small-study bias or selective reporting of secondary outcomes [42]. We included all study group comparisons in both the lumbar spine and femoral neck funnel plots in order to maximise interpretation. The observed tunnel effect on the femoral neck funnel plot may have resulted from the statistically significant effect sizes observed at this site within the high-impact only trials, compared with the findings from other protocols.

The findings from our review and meta-analysis are limited by trials recruiting highly selected samples of women of varying ages. In addition, the reporting of participants' use of oral contraception, which may have contributed to the research findings [43, 44], was poor. The trials were also variable in terms of study design, randomisation methods and treatment protocols.

We categorised the included exercise protocols according to the impact classifications described by Nikander et al. [6] and acceleration forces observed by Vainionpää et al. [17]. The majority of the exercise interventions of our included studies were undertaken 2 to 3 times per week. However, methods used to ensure adequate skeletal loading or progression of the exercises were in general not well reported. Only four of the included studies reported progressive elements to increase ground reaction force effects over the duration of the intervention [23, 26, 28, 29]. Trials of complex interventions such as exercise continue to present methodological challenges for meta-analysis.

Recommendations regarding optimum exercise for augmenting BMD in premenopausal women should include and clearly describe combinations of impact and resistance exercises that provide adequate skeletal loading and that are directly targeted at specific skeletal regions.

References

1. Peck WA, Burckhardt P, Christiansen C, Fleisch HA, Genant HK, Gennari C, Martin TJ, Martinin L, Morita R, Ogata A, Rapado A, Schulman I, Stern PH, Young RTT (1993) Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med* 94:646–650
2. Heaney RP, Abrams S, Wronski-Taylor B, Looker A, Marcus R, Matovic V, Weaver C (2000) Peak bone mass. *Osteoporos Int* 11:985–1009
3. Kohrt WM, Bloomfield SA, Little KD, Nelson ME, Yingling VR (2004) American College of Sports Medicine position stand on physical activity and bone health. *Med Sci Sports Exerc* 36:1985–1996
4. Lanyon LE, Rubin CT (1984) Static vs dynamic loads as an influence on bone remodelling. *J Biomech* 17:897–905
5. Frost HM (1988) Vital biomechanics: proposed general concepts for skeletal adaptations to mechanical usage. *Calcif Tissue Int* 42:145–156
6. Nikander R, Sievänen H, Heinonen A, Kannus P (2005) Femoral neck structure in adult female athletes subjected to different loading modalities. *J Bone Miner Res* 20:520–528
7. Martyn-St James M, Carroll S (2008) A meta-analysis of impact exercise on postmenopausal bone loss: the case for mixed loading exercise programmes. *Br J Sports Med*. doi:10.1136/bjism.2008.052704
8. Bailey CA, Brooke-Wavell K (2008) Exercise for optimising peak bone mass in women. *Proc Nutr Soc* 67:9–18
9. Higgins JPT, Green S (ed) (2008) *Cochrane Reviewers' Handbook 5.0.1* [updated September 2008]. In: The Cochrane library, issue 4. Wiley, Chichester
10. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup D (2000) Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Br J Surg* 87:1448–1454
11. Shea B, Bouter LE, Grimshaw JM, Francis D, Oritz Z, Wells GA, Tugwell PS, Boers M (2006) Scope for improvement in the quality of reporting of systematic reviews. From the Cochrane Musculoskeletal Group. *J Rheumatol* 33:9–15
12. Wallace BA, Cumming RG (2000) Systematic review of randomised trials of the effect of exercise on bone mass in pre- and postmenopausal women. *Calcif Tissue Int* 67:10–18
13. Wolff I, Van C, Kemper HCG, Kostense PJ, Twisk JWR (1999) The effect of exercise training programs on bone mass: a meta-analysis of published controlled trials in pre- and postmenopausal women. *Osteoporos Int* 9:1–12
14. Deeks JJ, Higgins JPT, Altman DG (ed) (2006) *Analysing and presenting results*. Cochrane handbook for systematic reviews of interventions 5.0.0 [updated February 2008]. Chapter 9. In: The Cochrane library, issue 4. Wiley, Chichester
15. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ (1996) Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 17:1–12
16. Shadish WR, Haddock CK (1994) Combining estimates of effect size. In: Cooper H, Hedges LV (eds) *The handbook of research synthesis*. New York, pp 261–284
17. Vainionpää A, Korpelainen R, Vihriälä E, Rinta-Paavola A, Leppäluoto J, Jämsä T (2006) Intensity of exercise is associated with bone density change in premenopausal women. *Osteoporos Int* 1–9
18. Higgins JPT, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. *BMJ* 327:557–560
19. Higgins JPT, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. *Stat Med* 21:1539–1558
20. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315:629–634
21. Bassey EJ, Rothwell MC, Littlewood JJ, Pye DW (1998) Pre- and postmenopausal women have different bone mineral responses to the same high-impact exercise. *J Bone Miner Res* 13:1805–1813
22. Friedlander AL, Genant HK, Sadowsky S, Byl NN, Gler CC (1995) A two-year program of aerobics and weight training enhances bone mineral density in young women. *J Bone Miner Res* 10:574–585
23. Heinonen A, Kannus P, Sievänen H, Oja P, Pasanen M, Rinne M, Uusi-Rasi K, Vuori I (1996) Randomised controlled trial of effect of high-impact exercise on selected risk factors for osteoporotic fractures. *Lancet* 348:1343–1347
24. Kato T, Terashima T, Yamashita T, Hatanaka Y, Honda A, Umemura Y (2006) Effect of low-repetition jump training on bone mineral density in young women. *J Appl Phys* 100:839–843
25. Sugiyama T, Yamaguchi A, Kawai S (2002) Effects of skeletal loading on bone mass and compensation mechanism in bone: a new insight into the mechanostat theory. *J Bone Miner Metab* 20:196–200
26. Vainionpää A, Korpelainen R, Leppäluoto J, Jämsä T (2005) Effects of high-impact exercise on bone mineral density: a randomized controlled trial in premenopausal women. *Osteoporos Int* 16:191–197
27. Weaver CM, Teegarden D, Lyle RM, McCave GP, McCabe L, Proulx W, Kern M, Sedlock D, Naderson DD, Hillberry BM, Peacock M, Johnston CC (2001) Impact of exercise on bone health and contraindication of oral contraceptive use in young women. *Med Sci Sports Exerc* 33:873–880
28. Winters-Stone KM, Snow CM (2006) Site-specific response of bone to exercise in premenopausal women. *Bone* 39:1203–1209

29. Winters KM, Titus M, Snow CM (1996) Progressive jump and lower body resistance training hip bone mass in premenopausal women. *Med Sci Sports Exerc* 31:S83
30. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gotzsche PC, Lang T, for the CONSORT Group (2001) The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 134:663–694
31. Martyn-St James M, Carroll S (2006) Progressive high-intensity resistance training and bone mineral density changes among premenopausal women: a meta-analysis. Evidence of discordant site-specific skeletal effects. *Sports Med* 36:683–704
32. Kleijnen J, Gøtzsche P, Kunz RA, Oxman AD, Chalmers I (1997) So what's so special about randomisation? In: Non-random reflections on health services research: on the 25th anniversary of Archie Cochrane's effectiveness and efficiency. BMJ Publishing, London, pp 93–106
33. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, Gluud C, Martin RM, Wood AJG, Sterne JAC (2008) Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 336:601–605
34. Akobeng AK (2005) Understanding randomised controlled trials. *Arch Dis Child* 90:840–844
35. Borer KT (2005) Physical activity in the prevention and amelioration of osteoporosis in women: interaction of mechanical, hormonal and dietary factors. *Sports Med* 35:779–830
36. Bassey EJ (1994) Increase in femoral bone density in young women following high-impact exercise. *Osteoporos Int* 4:72–75
37. Frost HM (1990) Skeletal structure adaptations to mechanical usage (SATMU); 1. Redefining Wolff's law: the bone modeling problem. *Anat Record* 226:403–413
38. Umemura Y, Nagasawa S, Honda A, Singh R (2008) High-impact exercise frequency per week or day for osteogenic response in rats. *J Bone Miner Metab* 26:456–460
39. Neville AM, Burrows M, Holder RL, Bird S, Simpson D (2003) Does lower-body BMD develop at the expense of upper-body BMD in female runners? *Med Sci Sports Exerc* 35:1733–1739
40. Moher D, Schulz KF, Altman D, for the CONSORT Group (2001) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 285:1987–1991
41. Sterne JAC, Egger M, Moher D (2008) Chapter 10: addressing reporting biases. In: Higgins JPT (ed) *Cochrane handbook for systematic reviews of interventions* version 5.0.1 [updated September 2008]. <http://www.cochrane-handbook.org>
42. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L (2008) Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 61:991–996
43. Hergenroeder AC, Smith EO, Shypailo R, Jones LA, Klish WJ, Ellis K (1997) Bone mineral changes in young women with hypothalamic amenorrhea treated with oral contraceptives, medroxyprogesterone, or placebo over 12 months. *Am J Obstet Gynecol* 176:1017–1025
44. Nappi CM, Sardo ADSM, Greco EM, Tommaselli GAM, Giordano EM, Guida MM (2005) Effects of an oral contraceptive containing drospirenone on bone turnover and bone mineral density. *Obstet Gynecol* 105:53–60