

Title: Exercise interventions for preventing and treating low bone mass in the forearm: A systematic review and meta-analysis

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Abstract

Objective: To examine the effectiveness of exercises for improving forearm bone mass.

Data sources: MEDLINE, EMBASE, CINAHL, AMED, Web of Science, and Cochrane CENTRAL were searched from their inception till December 2018.

Study selection: Eligibility included adults undertaking upper-limb exercise interventions [≥ 12 weeks] to improve bone mass.

Data extraction: Screening of titles/abstracts/full-texts and data extraction were undertaken independently by pairs of reviewers. Included studies were quality appraised using Cochrane risk of bias tool.

Data synthesis: Exercise interventions were classified into: 'resistance training' of high or low intensity (RTHI/RTLI, respectively), or 'impact'. Random-effects meta-analysis of the percentage change in forearm bone mass from baseline was conducted. Twenty-six studies were included in the review, of which 21 provided suitable data for meta-analysis. Methodological quality ranged from 'low' to 'unclear' risk of bias. Exercise generally led to increases (moderate-quality evidence) in forearm bone mass (standard mean difference [SMD]=1.27, 95% confidence interval [CI]=0.66, 1.88, overall effect Z-value=4.10, $p < 0.001$). RTHI (SMD=1.00, 95% CI=0.37, 1.62, Z-value=3.11, $p = 0.002$), and RTLI

(SMD=2.36, 95% CI=0.37, 4.36, Z-value=2.33, $p<0.001$) led to moderate increases in forearm bone mass. Improvements due to impact exercises (SMD=1.12, 95%CI= -1.27, 3.50, Z-value=0.92, $p=0.36$) were not statistically significant (low-quality evidence).

Conclusions: There is moderate-quality evidence that exercise is effective for improving forearm bone mass. There is moderate-quality evidence that upper body resistance exercise (RTHI/RTLI) promotes forearm bone mass, but low-quality evidence for impact exercise. Current evidence is equivocal regarding which exercise is most effective for improving forearm bone mass.

List of keywords: Bone density; osteoporosis; resistance training; upper limb

List of abbreviations

1RM	One-repetition maximum
BMC	Bone mineral content
BMD	Bone mineral density
CI	Confidence interval
CTs	Controlled trials
DXA	Dual energy X-ray absorptiometry
UK	United Kingdom
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
pQCT	Peripheral quantitative computed tomography
RCTs	Randomised controlled trials
RM	Repetition maximums
ROI	Region of interest

RT	Resistance training
RTHI	Resistance training, high intensity
RTLI	Resistance training, low intensity
SMD	Standardised mean difference
SPA	Single photon absorptiometry

Osteoporosis is a skeletal condition of bone fragility, resulting in a propensity to sustain fractures. Fragility fractures, defined as fractures resulting from low trauma, are extremely common, with an estimated 536,000 fractures occurring in the United Kingdom (UK) per annum, of which 69,000 represent fractures of the distal forearm.¹ Three million people are estimated to have osteoporosis in the UK and one in two women and one in five men aged 50 and over will experience a fragility fracture in their lifetime.² Specifically, one in three women will experience a wrist fracture.³ Fragility fractures can be devastating events, with hip and vertebral fractures leading to impaired quality of life, loss of independence, chronic pain, low mood and increased mortality risk.⁴⁻⁶ Wrist fractures may result in prolonged difficulty with activities of daily living; just under 50% of patients report functional impairment⁶ and over 60% report pain six months after fracture.⁷ Fragility fractures cost the UK National Health Service £4.4 billion/yr¹ and are one of the most common reasons for attending emergency departments.⁸ Post-fracture management constitutes a significant public health burden, and until recently it was assumed that the majority of this cost was attributable to hip fractures; however, recent research has identified that, partly due to their sheer volume, non-hip, non-vertebral fractures (including those of the wrist) use significantly more healthcare resources than hip fractures.⁹

Low bone mass is an important risk factor for fragility fracture. Bone mass is measured as bone mineral content (BMC) or bone mineral density (BMD), which accounts for 60% to 70% of variation in bone strength.¹⁰ The lifetime risk of an osteoporotic-related fracture increases 1.5 to 3 times with each SD decrease in BMD;¹¹ therefore, improving bone mass is an important goal of osteoporosis treatment and prevention in clinical practice. Strategies to increase or maintain bone mass can be pharmacological or nonpharmacological. Bone loss is exacerbated by disuse,¹² and conversely, loading of the skeleton promotes bone gain;¹³

exercise (which provides loading to the skeleton) is an important component of nonpharmacological interventions for improving bone health. However, at present, guidance on optimal exercise regimens for improving forearm bone mass is lacking and patients with, and who are at risk of, osteoporosis, have expressed preference for information about the optimal exercise regimens that will promote bone strength at different sites.^{14,15} There is currently no robust synthesised evidence regarding the effectiveness of exercise interventions on bone mass of the forearm. Reviews regarding the clinical effectiveness of exercise interventions in relation to bone mass generally have focused on the effects of exercise at the hip and spine^{16,17} and excluded trials relating to the effects in the upper limb. Others, which have included and considered the impact of exercise on forearm bone mass,^{18–20} have concluded conflicting results, possibly due to the non-exclusive focus on exercise interventions targeted at the upper limb. Furthermore, the specific types of exercises for optimal improvement in forearm bone mass are yet to be elucidated, and we can therefore not answer patient questions about optimum exercises to prevent wrist fracture. To address this gap in the literature, the aim of this study was to examine the effectiveness of exercise interventions targeted at the upper limb on forearm bone mass.

Specific objectives of this systematic review were to:

- a) summarise the evidence for the overall effects of exercise on forearm bone mass;
- b) determine the best type of exercise for improving forearm bone mass;
- c) identify gaps in the existing evidence, and promising exercise interventions that require investigation in future trials.

Methods

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for systematic reviews incorporating network meta-analyses for healthcare.²¹ An a priori protocol was established and registered with the international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017069545).

A comprehensive search strategy was developed with input from an information specialist, clinicians and academics. Six electronic databases (Medline, EMBASE, CINAHL, AMED, Cochrane Controlled Clinical Trials [CENTRAL], and Web of Science) were searched from their inception until December 2018 (search strategy: supplementary file). In addition, bibliographies of relevant review articles and selected articles were hand searched for potentially relevant trials.

Each identified trial was evaluated against the following predetermined selection criteria:

- (i) Study population: Adults, ≥ 18 yr.
- (ii) Intervention: Exercise intervention that include or target the upper limb to improve forearm bone mass. Interventions of <12 weeks' duration were excluded because it was unlikely that true bone mass changes would be detected earlier.
- (iii) Comparator: Control group of placebo or no intervention, or comparison with other interventions and therapies not specifically targeted at increasing bone mass at the forearm (e.g. balance exercises).
- (iv) Outcome measure: Percent change in bone mass, as assessed by dual energy X-ray absorptiometry (DXA), peripheral quantitative computed tomography (pQCT) or single photon absorptiometry (SPA).

The methodological quality of included trials was assessed using the Cochrane Collaboration's Risk of Bias tool.²² Trials were categorised as unclear, high or low risk of bias, based on: (i) sequence generation, (ii) allocation concealment, (iii) blinding of personnel, (iv) blinding of outcome assessor, (v) incomplete outcome data, (vi) selective outcome reporting, and (vii) other bias.

In pairs, reviewers (JF, KH, OB) independently evaluated the eligibility of identified trials. Using a customised, pre-tested and piloted data extraction form, risk of bias and data extraction for each included trial were performed and checked for completion and accuracy by pairs of reviewers (OB, JF, AE, KH). At each stage of the review (i.e. study selection, quality appraisal and data extraction process), discrepancies were resolved through discussion between pairs of reviewers or in review team meetings. For each included trial, extracted data included study demographics (rationale, study setting, participant characteristics), exercise intervention (mode of exercise, intensity, duration, number of sessions), control description, concurrent intervention, complications, adherence, attrition, length of follow up, outcomes and outcome measures. In instances of missing or incomplete data, additional information was requested from primary study authors.

Reviewers (JF, OB, AE), with subject knowledge of exercise and bone health, classified the exercise interventions to define subsets of exercise interventions to be analysed in the meta-analysis. These classifications were discussed and subsequently ratified by the review team (OB, JF, AE, KH, ZP). Classifications were as follows:

1. 'Resistance training' (RT) (isotonic/isokinetic concentric and eccentric, or isometric resistance training), further subdivided into:

1 a. Resistance training, high intensity (RTHI)

2 b. Resistance training, low intensity (RTL I)

3 2. ‘Impact’ exercise

4 The term ‘resistance training’ was used to reflect any form of muscle contraction against an
5 external resistance. The term ‘impact’ was used to reflect the action of a moving body part
6 coming into forcible contact with a stationary object.

7
8 Studies providing a point estimate of the outcome together with a measure of variability (e.g.
9 a mean and SD or confidence interval [CI]), or providing data to enable these to be derived,
10 were included in the analysis. Where studies reported multiple bone-mass outcomes at the
11 forearm, BMD-, BMC- and SPA-derived outcomes were prioritised (in that order) and used
12 for analysis. Where data for multiple bone sites within the forearm were reported, the 33%
13 radius was prioritised for analysis in line with recommendations of the International Society
14 for Clinical Densitometry.²³ Sensitivity analysis according to 33% radius was performed. The
15 difference between the percent change in the exercise group and the percent change in the
16 control group was used as the measure of effect. Where trials involved two treatment arms,
17 the “hypothesised” active treatment arm based on the primary study design was selected as
18 the intervention while the other arm was analysed as the control arm.

19
20 To obtain a summary estimate of treatment effects (with a 95% CI) of exercise on forearm
21 bone mass, a random effects meta-analysis was performed. The principal summary measure
22 used was a standardised mean difference (SMD) accounting for the different instruments,
23 scales and subscales used to measure BMD or BMC across the studies, thereby homogenising
24 outcomes onto a common scale. Estimates of effects (SMDs) were interpreted according to
25 Cohen’s rule of thumb, with values of 0.2, 0.5, and 0.8 indicative of small, moderate, and

large effects, respectively.²⁴ Pooled SMD estimates, along with 95% CIs, were computed for all exercise interventions. SMDs with 95% CIs that did not include the null value (of SMD=0, i.e. no difference in treatment effect), were classed as statistically significant. All analyses were performed using REVMAN (Version 5.3. Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014). To assess the robustness of the findings, sensitivity analysis based on risk of bias was planned, however not performed, due to most studies having similar (unclear) risk of bias. Subgroup analyses were performed by exercise classification and menopausal status (pre- and post-menopausal). Assessment of the overall quality of evidence per outcome was performed using the GRADE approach.²⁵

Results

The literature search yielded 2180 unique citations, of which 165 full-text articles were selected for full review. No new studies were identified by hand searching of references or grey literature. The study flow chart is presented in Figure 1. Of the 165 full-text articles, 34 articles were subjected to quality assessment and data extraction. Eight articles could not be included in the review due to being duplicate reports of the same trial.

Characteristics of the 26 included trials are presented in Table 1. The length of exercise intervention period ranged from four months²⁶ to three yr²⁷ with 13 of the included studies involving exercise interventions that were ≥ 12 months in duration.²⁷⁻³⁹ Most of the trials were conducted in North America (n=12), and Europe (n=9). Trials recruited participants mostly from the community or outpatient departments of hospitals and rehabilitation centres.

Seven trials included participants with low bone-health (diagnosis of osteopaenia or osteoporosis),^{31,32,35,36,40–42}, while 13 trials failed to specify whether participants with low bone density were included.^{26–28,30,31,38,42–48} Of the 26 trials, six investigated the effects of exercise on forearm bone mass in premenopausal women,^{26,34,37,45,46,48} 18 sampled postmenopausal women^{27–32,35,36,38–43,47,49–51} and two included both pre- and post-menopausal populations.^{33,44} A priori, studies which recruited male participants were not excluded. Two trials^{26,42} with male participants met the eligibility criteria and were included in the review. One trial investigated exercise the effects in men alone,²⁶ while men (39.3% male) and women were included in the trial by Duckham et al.⁴² These two trials with men did not contribute data to the meta-analysis (supplementary file, Table S1, lists eligible studies not included in the meta-analysis with reasons). The trial by Duckham et al.⁴² did not contain suitable data for inclusion in the meta-analysis. The study by Fujimura²⁶ was excluded owing to these data being the only data on males, and because including the data might have added further heterogeneity into the meta-analysis. Both studies are, however, included in the narrative analysis.

Risk of bias outcomes are presented in Figures S1a and S1b of the supplementary file. A high risk of bias was considered present most frequently in up to six trials (~22% of trials) in relation to selection bias (i.e. lack of randomisation and allocation concealment). Twenty-two trials (~80%) did not adequately report blinding of participants and personnel and were assessed as having unclear risk of performance bias. Outcome assessment procedures were reported as blinded in only five (~20%) of the trials as the reporting of most of the trials did not provide sufficient information to accurately assess blinding of outcome assessment procedures, thus generating a large proportion of “unclear” responses in 21 (~75%) trials.

Overall, only five trials were of high quality with up to 70% of risk of bias items (i.e. $\geq 5/7$ items) classed as low risk.^{35,36,38,49,51}

Following classification according to exercise, 16 studies were classified as RTHI,^{26,28–32,34,35,39,40,45–47,49–51} since they used fixed or free-weight resistance training that induced fatigue within ≤ 12 continuous repetitions and/or a resistance equivalent to $\geq 70\%$ of one repetition maximum (1RM) (Table 2a). Populations (n=897) mostly comprised of postmenopausal women (n=759), who had been previously sedentary. Dose and intensity of exercise were described using sets, repetitions, and repetition maximums (RM) or as a percentage of 1RM. All RTHI studies involved one or more sets of 8 to 12 repetitions, performed to fatigue or at an intensity equivalent to 70% to 90% 1RM, and were progressed to ensure continuous adaptation, often by increasing the load once the required repetitions were achieved. These sets, repetitions, and loads were consistent across studies apart from two that involved a periodised loading pattern, where higher repetitions and lower loads were interleaved with lower repetitions and higher loads.^{39,45} One study failed to provide specific details on sets, repetitions and load.⁴⁷ Studies in the RTHI group were mostly centre-based, using fixed-resistance machines (e.g. lateral pulldown), or free weights (e.g. dumbbell row), and included combinations of biceps curl, triceps extension, triceps push down, shoulder press, bench press, wrist curl, lateral pull down, upright row, front shoulder raise, and row.

Eight studies investigated the effects of low-intensity resistance training on forearm bone mass (Table 2b).^{27,33,36,38,41–44} Studies that did not meet the ‘high intensity’ criteria described above were classed as ‘low intensity’. RTLI participants (n=1222), were nearly all postmenopausal women, with some comprising both pre- and post-menopausal women.^{33,44}

RTLI studies mostly recruited sedentary participants and involved centre-based^{41,44} or centre- and home-based exercises.^{36,38,42,43} Only one study was completely home-based.²⁷ Dose and intensity of the exercise programmes and/or loading patterns were described using frequency (sets, repetitions) and time. Frequency of exercise loading ranged from one to three sets of 10 to 25 repetitions.^{33,36,43} Three of the RTLI trials reported the exercise loading pattern in terms of total time spent per session (10-20 min).^{38,41,44} All RTLI interventions consisted of isoinertial concentric and eccentric contractions using a low intensity or load, with resistance applied using body weight, fixed resistance machines/free weights,³³ elastics such as Thera-Band® elastic tubing,^{27,42} gym-based or sports equipment, or a mixture of these approaches.^{36,38,41,43,44}

Two studies (n=131 participants) examined the effect of exercise interventions involving impact on forearm bone mass.^{37,48} Both studies included premenopausal populations without history of regular exercise within six months to two years preceding enrolment (Table 2c). The exercise programmes involved impacting the hand and wrist by dropping onto a wall with an outstretched arm. Impact load ranged from 47%⁴⁸ to 90% body mass³⁷ and repetitions were progressed to 36 to 40 per session.

Exercise compliance and adherence were either expressed as the percentage of sessions attended or as the percentage of the exercise regime adhered to, based on self-report data, and were reported in all but two studies.^{30,42} Across RTHI/RTLI and impact exercise trials, adherence ranged from 40%⁴³ to 90%.⁵⁰ Loss to follow-up (i.e. participants assigned to study groups versus those analysed at end-point assessment) ranged from 0%^{35,41} to 55%.⁴⁶ Only one trial failed to report loss to follow-up at any stage of the trial.³⁸

Fourteen studies reported that the exercise was partly supervised (three RTHI, four RTLI)^{27,32–34,36,39,42} or fully supervised (six RTHI, one RTLI).^{28,29,31,35,38,45,51} Exercise sessions in both impact trials were home-based and unsupervised.^{37,48} The remaining studies did not describe supervision.

In two RTHI studies,^{29,46} the contralateral limb was used as the control. Participants acted as their own control in one RTLI study.⁴⁴ Five other studies (4 RTHI^{31,38–40} and one RTLI)³⁶ involved a comparison group rather than a control group. For those studies with a ‘true’ control group, participants in three studies, all RTHI,^{34,49,51} performed ‘sham’ exercise, in the form of stretching and relaxation. One RTHI study failed to describe the control group instruction.⁴⁴ In the remaining studies, including both impact exercise trials, participants were requested to continue with their usual lifestyle.

Alongside the prescribed exercise, participants in some studies (four RTHI, two RTLI) received calcium supplements.^{26,28,41,43,45,47} Others (three RTHI, two RTLI) received calcium and vitamin D supplements;^{32,36,39,50,51} or dietary advice to take more calcium.³⁰ In one RTHI study, exercise was combined with a daily dose of 0.625 mg conjugated oestrogen.³¹ Across these studies, both the exercise intervention group and the control/comparison group were given the concurrent interventions (i.e. calcium/vitamin D supplements/oestrogen), thus minimising the confounding effect of the intake.

Fifteen studies measured bone mass using DXA,^{26,28–34,36,37,39,42,45,48,50} six used pQCT,^{35,40,43,44,49,51} and five used SPA.^{27,31,38,41,47} Of the DXA studies, there was variation in the site of measurement, from total forearm bone density.^{32,46} one-third forearm,^{28–30,32,36,50} distal/ultra-distal forearm^{28–30,32–34,36,37,39,42,43,45} and mid-radius.^{26,28,29,34} Accuracy of the

assessment tool was reported in all studies (mainly using coefficient of variance), apart from three.^{32,36,39} Instrument precision for the primary outcomes ranged from 0.3%³⁴ to 10.2%.³⁵ None of the studies assessed fracture incidence as an outcome.

In the RTHI group, two studies that included lower limb interventions, including running and jumping, reported falls during the exercise sessions with 3.6% of exercisers³⁵ and 2.1% of exercisers³⁹ reporting falls during the intervention period. Reported adverse events were mostly a consequence of lower-limb components of the exercise intervention. For example, four participants (12.5%) from the training groups in Karinkanta et al.³⁵ consulted a physician due to lower-limb musculoskeletal injuries. Karinkanta et al also reported 10 patients with 'overuse' symptoms at unspecified sites.³⁵ Furthermore, three studies^{29,32,49} reported several minor musculoskeletal complaints, such as muscle soreness and strains. Only one study reported a wrist injury but without further details.²⁸ Other RTHI studies reported no adverse events.^{28,29,31,32,34,35,39,40,45–47,49,50} In the RTLI group, several participants reported mild tendonitis and one participant broke her ankle while walking.²⁹ Other studies, with the exception of Adami et al.,⁴³ failed to report adverse events in relation to exercise. For the impact exercises, mild to moderate soreness during the early intervention period was reported by five participants (21%) in Wang et al.,⁴⁸ but no adverse events were reported by Greenway et al.³⁷

Twenty-one trials involving 1619 participants provided sufficient data for inclusion in the meta-analysis. All the RTHI trials included in this review were incorporated into the meta-analysis. However, over half of the data for the RTLI exercises could not be pooled statistically. Exercise was generally associated with relative increases in forearm bone mass (SMD=1.27, 95% CI=0.66, 1.88, overall effect Z-value=4.10, p<0.001). Sensitivity analysis

for studies which used 33% radius as the region of interest (ROI) (SMD=1.43, 95% CI=0.50, 2.36, overall effect Z-value=3.02, $p<0.001$) were consistent with overall effects of exercises at all ROIs. Compared to control/comparators, resistance training, RTHI (SMD=1.00, 95%CI=0.37, 1.62, Z value=3.11, $p=0.002$) and RTLI (SMD=2.36, 95% CI=0.37, 4.36, Z value=2.33, $p<0.001$) both led to significant increases in forearm bone mass; however, RTLI exercises led to greater improvements than RTHI. Impact exercises also conferred improvements on bone mass (SMD=1.12, 95% CI=-1.27, 3.50, Z value=0.92, $p=0.36$) compared to control/comparators, but these effects were not statistically significant. Forrest plots of analysis are shown in Figure 2a-e. Postmenopausal women were more likely to benefit from exercise regimes for forearm bone mass (SMD=1.64, 95% CI=0.92, 2.36, Z value=4.46, $p<0.001$) compared to premenopausal women (SMD=0.22, 95% CI=-1.01, 1.45, Z value=0.35, $p=0.72$). Furthermore, subgroup analysis for studies on people with low bone mass/osteoporosis compared to populations with “mixed/unknown” bone-health status at the start of respective trials were performed. Forest plots of sensitivity and further subgroup analyses are presented in Figure 3. A summary of findings of all the included studies with respect to effects of exercise on forearm bone mass is presented in Table 3.

Discussion

We have reported the first systematic review and meta-analysis to exclusively focus on exercise interventions targeted at improving forearm bone mass. Based on 26 randomised controlled trials (RCTs) and controlled trials (CTs), there was a statistically significant, though modest, effect of targeted upper-limb exercise on forearm bone mass. All types of exercise, including RTHI, RTLI and impact exercise improved bone mass at the forearm, but the strength of evidence was moderate for RTHI and RTLI and low for impact exercise. From

subgroup analysis, significant changes in bone mass were demonstrated for postmenopausal, but not premenopausal women. Adverse events relating to the upper-limb exercises, when reported, were generally minor musculoskeletal complaints.

In a previous meta-analysis, ‘aerobic exercise’ was effective in increasing BMD at the wrist, but resistance training was ineffective;²⁰ however only three studies in their meta-analysis targeted the forearm or arm, compared to 21 in the current study. In another meta-analysis, it was found that exercise did not maintain cortical or trabecular volumetric BMD of the radius.¹⁸ These prior findings may conflict with the results of present study due the requirement, in the current study, to include only targeted upper-limb exercise. More evidence has also been synthesised in addition to those that were available previously.

The finding that RTLI conferred greater benefits than RTHI does not support the results from previous meta-analyses, where high-joint magnitude forces (high-intensity resistance training) induced greater osteogenic effects in the lower limb compared to low-joint magnitude forces.^{16,17,54,55} The diversity of studies in the RTLI and RTHI groups, in terms of exercise adherence, exercise characteristics, and adjunct therapy, might have affected overall effects. Furthermore, although classified as low intensity, the exercises in the RTLI group were generally more novel and varied in terms of strain distributions and strain rates. For instance, in the studies of Ayalon et al.⁴¹ and Adami et al.,⁴³ exercises were included that specifically targeted the wrist and forearm in a way that was unique in terms of being different than everyday movement patterns.^{41,43} Bone has been found to adapt not only to dynamic loads of high strain magnitude, but also to high strain rates, rapid strain reversal and unusual frequency distributions.^{56,57} It is, therefore, possible that the uniqueness of the interventions in the RTLI group might have contributed to the positive effects on forearm

bone mass. An alternative explanation could be that all studies in the RTHI group employed a combination of upper and lower body exercise, with loading of the upper limb and radius often only playing a small part in the overall training programme,^{32,34,35,47} whereas more studies in the RTLI group targeted the upper extremity specifically.^{29,36,41,43}

Upper-limb exercise, regardless of exercise type, was effective for improving bone mass in postmenopausal women, but ineffective for premenopausal women. It is possible that the exercise was not of sufficient strain to induce an osteogenic effect among the premenopausal women, since the women in the included trials were all healthy, with no known or diagnosed risk factors affecting bone health. Similarly, in a previous meta-analysis, impact exercise was shown to be less effective in preventing bone loss at the lumbar spine for premenopausal women than it was for postmenopausal women.⁵⁸ Although previous studies in premenopausal female and younger male athletes engaged in predominantly upper-limb exercise have demonstrated greater BMD than controls,⁵⁹ or greater BMD in the dominant compared with non-dominant arm,^{60–63} the force and impact in these studies may have been greater than the force/impact of the interventions included in this meta-analysis.

Study limitations

This is the first systematic review to focus on forearm bone-mass accrual as a result of exercise interventions. We have conducted a rigorous search for all available trials in which the effect of exercise on forearm bone mass has been investigated. However, several limitations, mainly due to the limited evidence of the primary studies included in this review, are worthy of mention. The use of change in bone mass, as measured by DXA, pQCT and SPA, as an outcome measure in this review, might imply that the full effects of exercise on

forearm bone mass might have been missed, since BMD has been shown to only partly measure bone strength, and not to be sensitive enough to detect exercise-related improvements. Bone has other properties such as stiffness, ability to absorb energy, elasticity, strength and geometric properties, for which BMD assessment via DXA does not account.^{18,51} Distinguishing losses and gains in cortical and trabecular bone, and measuring bone geometry and structural strength through, for instance, pQCT, might have provided different results.^{64,65} There were, however, too few studies, in which pQCT-derived outcomes were reported. Another limitation was that the quality of data reporting from included trials was poor, ranging mostly from low to moderate. Quality was especially impacted by high or unclear risk of bias regarding random sequence generation and incomplete outcome data, and should, therefore, be considered when interpreting the main findings. In the current systematic review, 14 studies were RCTs and 12 were CTs. If trials are not RCTs, then effects can be overestimated.^{54,55,66} Only two studies were blinded to study participants and personnel,^{38,51} although it is extremely difficult to use a double-blind research design for interventions involving exercise. In some studies, only participants who had complied with the exercise programme were included in the analysis,^{27,29,67} rather than an intention-to-treat analysis being undertaken, which can result in an overestimation of the treatment effect. A high dropout can also mean that confounding factors might not be counterbalanced despite the initial randomisation. The inconsistencies in compliance, dropout rates and methods of analysing follow-up data between studies could, therefore, have affected the trial findings. Compensatory effects (i.e. the exercise group doing less physical activity due to the intervention) is a further possible source of bias.

Although the data from the meta-analyses seem to support the benefit of exercise for bones of the forearm, there was high heterogeneity ($I^2=96\%$, 94%, 99%, 96% for overall effect, RTHI,

RTLI, and impact exercises, respectively), which may largely be due to the inherently high variations in the exercise interventions (multiple modes/exercise type, dose, intensity) across included trials. In classifying the exercise interventions, we had considered the probable effects of the different exercise types on bone accrual. Even though the studies were classified according to exercise characteristics, there was considerable diversity in how the load was applied to the bone. RT groups consisted of isoinertial and isokinetic muscle contraction, as well as exercise using elastics. With isoinertial resistance exercise, tension forces are generated by the muscle, and transmitted via ligaments and tendons to the bone.⁶⁸ With isokinetic training, there may be differences to how the bone responds, since differences exist in motor recruitment, and neuromuscular adaptation mechanisms when compared to isoinertial training.^{69,70} With elastics, the resistance differs throughout the range of motion, being greater the further away the load is from the fulcrum (i.e. when the elastic is elongated), and electromyographic activity may differ from isoinertial exercise.⁷¹ Further research on the effect of different types of resistance training on forearm bone mass could be carried out. Furthermore, only two studies investigated the effect of impact exercises and were pooled together in a subgroup analysis. In previous literature, exercises with higher (than habitual) levels of impact have been shown to induce significant levels of bone density adaptation but these are in lower limb bone sites.⁷²⁻⁷⁵ Even though, the force magnitudes in these two studies may be comparable to those used in lower limb literatures, the validity of the current analysis may be limited, due to small sample sizes in those two studies. It could also not be determined, based on these two studies alone, whether there was a threshold for how much impact, in terms of magnitude of force, was necessary to induce significant levels of bone density adaptation in the forearm.

Further research

The findings of this review suggest that targeted forearm RTHI and RTLI may improve forearm bone mass. Although RTLI appeared more effective, the current evidence base is not sufficiently strong to prioritise RTLI over RTHI. Optimal dose of resistance exercise for forearm bone mass accrual should be explored in future trials. Clinical interpretation of our findings is somewhat limited due to the large number of studies that did not report adverse events in relation to upper-limb exercises, and that no studies included fracture incidence as an outcome. Changes in bone mass at the forearm may not translate to clinically and statistically significant fracture reduction. We recommend that future trials of exercise interventions report incident fractures alongside bone measurements. No studies included a follow-up period after the intervention, so it is not possible to conclude whether the change in bone mass was sustainable, or indeed, if the exercises themselves are sustainable. Further studies are needed on safety and effectiveness of upper-limb-specific resistance and impact exercises. There were sparse data involving men in this review. Future research should explore the effectiveness, acceptability and sustainability of exercise for forearm bone mass accrual in men.

Accumulating evidence suggests that muscle and bone work in unison, mechanically through high strains imposed on the bone due to muscle activation, and at the molecular level through cell-signalling mechanisms and cross talk.^{76,77} Although the evidence on mechano-adaptation is accumulating, the precise mechanism of how forearm bone adapts to conventional resistance training programmes is also an area where further research is needed. Few studies (only two trials in this review) investigated the effect of ‘impact’ exercise on forearm bone mass. Owing to the need for high intensity and novel loading patterns to incur an osteogenic effect, lower body impact exercises have been found to be effective for improving BMD at

the lumbar spine and femoral neck of premenopausal women and other populations.^{64,78,79,75,80}

Further research into the effect of exercises involving impact or a combination of resistance training with high-impact loading on forearm bone is warranted.

Conclusions

This is the first systematic review and meta-analysis to examine the effectiveness of exercise interventions for enhancing bone mass of the forearm in adults. There is moderate-quality evidence that resistance training with high or low intensity induces significant effects on forearm bone mass; however, current estimates of effects for most exercise regimes varied in magnitude and were imprecise. Future research into optimal dose and application of exercise interventions for forearm bone mass is needed. In view of the number of possible avenues for further research, future trials will benefit from prior consensus with clinicians, patients and exercise experts in order to prioritise aspects of exercise interventions to be considered for targeting and enhancing forearm bone mass.

Highlights (optional)

- This systematic review and meta-analysis examined the effectiveness of exercise interventions for improving bone mass of the forearm in adults.
- There is moderate-quality evidence that resistance exercise improves forearm bone mass but low-quality evidence for impact exercise.
- Available evidence remains equivocal on the optimal dose, intensity and frequency of promising exercise interventions for forearm bone mass.

References

1. Svedbom A, Hernlund E, Ivergård M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: a compendium of country-specific reports. Arch. Osteoporos. [Internet]. 2013;8:137. Available from: <http://link.springer.com/10.1007/s11657-013-0137-0>
2. Van Staa TP, Dennison EM, Leufkens HGM, Cooper C. Epidemiology of fractures in England and Wales. Bone. 2001;29:517–22.
3. Ahmed LA, Schirmer H, Bjørnerem Å, Emaus N, Jørgensen L, Størmer J, et al. The gender- and age-specific 10-year and lifetime absolute fracture risk in Tromsø, Norway. Eur. J. Epidemiol. [Internet]. 2009;24:441–8. Available from: <http://link.springer.com/10.1007/s10654-009-9353-8>
4. Williamson S, Landeiro F, McConnell T, Fulford-Smith L, Javaid MK, Judge A, et al. Costs of fragility hip fractures globally: a systematic review and meta-regression analysis. Osteoporos. Int. [Internet]. 2017;28:2791–800. Available from: <http://link.springer.com/10.1007/s00198-017-4153-6>
5. Borgström F, Zethraeus N, Johnell O, Lidgren L, Ponzer S, Svensson O, et al. Costs and quality of life associated with osteoporosis-related fractures in Sweden. Osteoporos. Int. [Internet]. 2006;17:637–50. Available from: <http://link.springer.com/10.1007/s00198-005-0015-8>
6. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet [Internet]. 2002;359:1761–7. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/12049882>
7. Moore CM, Leonardi-Bee J. The prevalence of pain and disability one year post fracture of the distal radius in a UK population: A cross sectional survey. BMC Musculoskelet. Disord. [Internet]. 2008;9:129. Available from:

1 <https://bmcmusculoskeletdisord.biomedcentral.com/articles/10.1186/1471-2474-9-129>

2 8. Nellans KW, Kowalski E, Chung KC. The epidemiology of distal radius fractures.

3 Hand Clin. [Internet]. 2012;28:113–25. Available from:

4 <https://linkinghub.elsevier.com/retrieve/pii/S0749071212000029>

5 9. Ioannidis G, Flahive J, Pickard L, Papaioannou A, Chapurlat RD, Saag KG, et al. Non-

6 hip, non-spine fractures drive healthcare utilization following a fracture: the Global

7 Longitudinal Study of Osteoporosis in Women (GLOW). Osteoporos. Int. [Internet].

8 2013;24:59–67. Available from: <http://link.springer.com/10.1007/s00198-012-1968-z>

9 10. Ammann P, Rizzoli R. Bone strength and its determinants. Osteoporos. Int. [Internet].

10 2003;14:13–8. Available from: <http://link.springer.com/10.1007/s00198-002-1345-4>

11 11. Cummings SR, Browner W, Cummings SR, Black DM, Nevitt MC, Browner W, et al.

12 Bone density at various sites for prediction of hip fractures. Lancet [Internet].

13 1993;341:72–5. Available from:

14 <https://linkinghub.elsevier.com/retrieve/pii/0140673693925558>

15 12. Rittweger J, Simunic B, Bilancio G, Gaspare De Santo N, Cirillo M, Biolo G, et al.

16 Bone loss in the lower leg during 35 days of bed rest is predominantly from the

17 cortical compartment. Bone [Internet]. 2009;44:612–8. Available from:

18 <https://linkinghub.elsevier.com/retrieve/pii/S8756328209000118>

19 13. Sugiyama T, Yamaguchi A, Kawai S. Effects of skeletal loading on bone mass and

20 compensation mechanism in bone: a new insight into the “mechanostat” theory. J.

21 Bone Miner. Metab. [Internet]. 2002;20:196–200. Available from:

22 <http://link.springer.com/10.1007/s007740200028>

23 14. Paskins Z, Jinks C, Mahmood W, Jayakumar P, Sangan CB, Belcher J, et al. Public

24 priorities for osteoporosis and fracture research: results from a general population

25 survey. Arch. Osteoporos. [Internet]. 2017;12:45. Available from:

1 <http://link.springer.com/10.1007/s11657-017-0340-5>

- 2 15. Raybould G, Babatunde O, Evans AL, Jordan JL, Paskins Z. Expressed information
3 needs of patients with osteoporosis and/or fragility fractures: a systematic review.

4 Arch. Osteoporos. [Internet]. 2018;13:55. Available from:

5 <http://link.springer.com/10.1007/s11657-018-0470-4>

- 6 16. Howe TE, Shea B, Dawson LJ, Downie F, Murray A, Ross C, et al. Exercise for
7 preventing and treating osteoporosis in postmenopausal women. Cochrane Database
8 Syst. Rev. [Internet]. 2011; Available from:

9 <http://doi.wiley.com/10.1002/14651858.CD000333.pub2>

- 10 17. Marques EA, Mota J, Carvalho J. Exercise effects on bone mineral density in older
11 adults: A meta-analysis of randomized controlled trials. Age (Omaha). 2012;34:1493–
12 515.

- 13 18. Polidoulis I, Beyene J, Cheung AM. The effect of exercise on pQCT parameters of
14 bone structure and strength in postmenopausal women—a systematic review and meta-
15 analysis of randomized controlled trials. Osteoporos. Int. [Internet]. 2012;23:39–51.

16 Available from: <http://link.springer.com/10.1007/s00198-011-1734-7>

- 17 19. Bérard A, Bravo G, Gauthier P. Meta-analysis of the effectiveness of physical activity
18 for the prevention of bone loss in postmenopausal women. Osteoporos. Int.

19 1997;7:331–7.

- 20 20. Bonaiuti D, Shea B, Iovine R, Negrini S, Welch V, Kemper HH, et al. Exercise for
21 preventing and treating osteoporosis in postmenopausal women [Internet]. In: Bonaiuti
22 D, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley &
23 Sons, Ltd; 2002. p. CD000333. Available from:

24 <http://doi.wiley.com/10.1002/14651858.CD000333>

- 25 21. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The

- PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. *Ann. Intern. Med.* [Internet]. 2015;162:777. Available from: <http://annals.org/article.aspx?doi=10.7326/M14-2385>
22. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* [Internet]. 2011;343:d5928–d5928. Available from: <http://www.bmj.com/cgi/doi/10.1136/bmj.d5928>
23. Densitometry TIS for C. 2015 ISCD Official Positions – Adult [Internet]. 2015; Available from: <http://www.iscd.org/official-positions/2015-iscd-official-positions-adult/>
24. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, New York: Lawrence Earlbaum Associates; 1988.
25. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* [Internet]. 2008;336:924–6. Available from: <http://www.bmj.com/lookup/doi/10.1136/bmj.39489.470347.AD>
26. Fujimura R, Ashizawa N, Watanabe M, Mukai N, Amagai H, Fukubayashi T, et al. Effect of resistance exercise training on bone formation and resorption in young male subjects assessed by biomarkers of bone metabolism. *J. Bone Miner. Res.* 1997;12:656–62.
27. Preisinger E, Alacamlioglu Y, Pils K, Saradeth T, Schneider B. Therapeutic exercise in the prevention of bone loss. A controlled trial with women after menopause. *Am. J. Phys. Med. Rehabil.* [Internet]. 1995;74:120–3. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7710725>

28. Kerr D, Ackland T, Maslen B, Morton A, Prince R. Resistance Training over 2 Years Increases Bone Mass in Calcium-Replete Postmenopausal Women. *J. Bone Miner. Res.* [Internet]. 2001;16:175–81. Available from: <http://doi.wiley.com/10.1359/jbmr.2001.16.1.175>
29. Kerr D, Morton A, Dick I, Prince R. Exercise effects on bone mass in postmenopausal women are site-specific and load-dependent. *J. Bone Miner. Res.* [Internet]. 1996;11:218–25. Available from: <http://doi.wiley.com/10.1002/jbmr.5650110211>
30. Kohrt WM, Ehsani AA, Birge SJ. Effects of exercise involving predominantly either joint-reaction or ground-reaction forces on bone mineral density in older women. *J. Bone Miner. Res.* [Internet]. 1997;12:1253–61. Available from: <http://doi.wiley.com/10.1359/jbmr.1997.12.8.1253>
31. Notelovitz M, Martin D, Tesar R, Khan FY, Probart C, Fields C, et al. Estrogen therapy and variable-resistance weight training increase bone mineral in surgically menopausal women. *J. Bone Miner. Res.* [Internet]. 1991;6:583–90. Available from: <http://doi.wiley.com/10.1002/jbmr.5650060609>
32. Waltman NL, Twiss JJ, Ott CD, Gross GJ, Lindsey AM, Moore TE, et al. The effect of weight training on bone mineral density and bone turnover in postmenopausal breast cancer survivors with bone loss: A 24-month randomized controlled trial. *Osteoporos. Int.* 2010;21:1361–9.
33. Heinonen A, Oja P, Sievanen H, Pasanen M, Vuori I. Effect of two training regimens on bone mineral density in healthy perimenopausal women: a randomized controlled trial. *J. Bone Miner. Res.* 1998;13:483–190.
34. Heinonen A, Sievänen H, Kannus P, Oja P, Vuori I. Effects of unilateral strength training and detraining on bone mineral mass and estimated mechanical characteristics of the upper limb bones in young women. *J. Bone Miner. Res.* [Internet].

- 1996;11:490–501. Available from: <http://doi.wiley.com/10.1002/jbmr.5650110410>
35. Karinkanta S, Heinonen A, Sievänen H, Uusi-Rasi K, Pasanen M, Ojala K, et al. A multi-component exercise regimen to prevent functional decline and bone fragility in home-dwelling elderly women: Randomized, controlled trial. *Osteoporos. Int.* 2007;18:453–62.
36. Judge JO, Kleppinger A, Kenny A, Smith J-A, Biskup B, Marcella G. Home-based resistance training improves femoral bone mineral density in women on hormone therapy. *Osteoporos. Int.* [Internet]. 2005;16:1096–108. Available from: <http://link.springer.com/10.1007/s00198-004-1816-x>
37. Greenway KG, Walkley JW, Rich PA. Impact exercise and bone density in premenopausal women with below average bone density for age. *Eur. J. Appl. Physiol.* 2015;115:2457–69.
38. Prince RL, Smith M, Dick IM, Price RI, Webb PG, Henderson NK, et al. Prevention of postmenopausal osteoporosis. *N. Engl. J. Med.* [Internet]. 1991;325:1189–95. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJM199110243251701>
39. Kemmler W, Lauber D, Weineck J, Hensen J, Kalender W, Engelke K. Benefits of 2 years of intense exercise on bone density, physical fitness, and blood lipids in early postmenopausal osteopenic women. *Arch. Intern. Med.* [Internet]. 2004;164:1084. Available from: <http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.164.10.1084>
40. Stolzenberg N, Belavý DL, Beller G, Armbrecht G, Semler J, Felsenberg D. Bone strength and density via pQCT in post-menopausal osteopenic women after 9 months resistive exercise with whole body vibration or proprioceptive exercise. *J. Musculoskelet. Neuronal Interact.* 2013;13:66–76.
41. Ayalon J, Simkin A, Leichter I, Raifmann S. Dynamic bone loading exercises for

- 1 postmenopausal women: effect on the density of the distal radius. Arch. Phys. Med.
- 2 Rehabil. [Internet]. 1987;68:280–3. Available from:
- 3 <http://www.ncbi.nlm.nih.gov/pubmed/3579532>
- 4 42. Duckham RL, Masud T, Taylor R, Kendrick D, Carpenter H, Iliffe S, et al.
- 5 Randomised controlled trial of the effectiveness of community group and home-based
- 6 falls prevention exercise programmes on bone health in older people: The ProAct65+
- 7 bone study. Age Ageing. 2015;44:573–9.
- 8 43. Adami S, Gatti D, Braga V, Bianchini D, Rossini M. Site-specific effects of strength
- 9 training on bone structure and geometry of ultradistal radius in postmenopausal
- 10 women. J. bone Miner. Res. [Internet]. 1999;14:120–4. Available from:
- 11 <http://www.ncbi.nlm.nih.gov/pubmed/9893073>
- 12 44. Danz AM, Zittermann A, Schiedermaier U, Klein K, Hötzel D, Schönau E. The effect
- 13 of a specific strength-development exercise on bone mineral density in perimenopausal
- 14 and postmenopausal women. J. Women's Heal. [Internet]. 1998;7:701–9. Available
- 15 from: <http://www.liebertonline.com/doi/abs/10.1089/jwh.1998.7.701>
- 16 45. Dorneman TM, McMurray RG, Renner JB, Anderson JJB. Effects of high-intensity
- 17 resistance exercise on bone mineral density and muscle strength of 40- 50-year-old
- 18 women. J. Sports Med. Phys. Fitness. 1997;3:246–51.
- 19 46. Nickols-Richardson SM, Miller LE, Wootten DF, Ramp WK, Herbert WG. Concentric
- 20 and eccentric isokinetic resistance training similarly increases muscular strength, fat-
- 21 free soft tissue mass, and specific bone mineral measurements in young women.
- 22 Osteoporos. Int. 2007;18:789–96.
- 23 47. Rikli RE, McManis BG. Effects of exercise on bone mineral content in
- 24 postmenopausal women. Res. Q. Exerc. Sport [Internet]. 1990;61:243–9. Available
- 25 from: <http://www.tandfonline.com/doi/abs/10.1080/02701367.1990.10608686>

48. Wang M, Salem GJ. The relations among upper-extremity loading characteristics and bone mineral density changes in young women. *Bone* [Internet]. 2004;34:1053–63. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S8756328204000602>
49. Liu-Ambrose TYL, Khan KM, Eng JJ, Heinonen A, McKay HA. Both resistance and agility training increase cortical bone density in 75- to 85-year-old women with low bone mass. *J. Clin. Densitom.* [Internet]. 2004;7:390–8. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S109469500660022X>
50. Bembien DA, Fettaers NL, Bembien MG, Nabavi N, Koh ET. Musculoskeletal responses to high- and low-intensity resistance training in early postmenopausal women. *Med. Sci. Sports Exerc.* [Internet]. 2000;32:1949–57. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11079527>
51. Duff WRD, Chilibeck PD, Candow DG, Gordon JJ, Mason RS, Taylor-Gjevve R, et al. Effects of ibuprofen and resistance training on bone and muscle. *Med. Sci. Sport. Exerc.* [Internet]. 2017;49:633–40. Available from: <http://insights.ovid.com/crossref?an=00005768-201704000-00002>
52. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *Br. Med. J.* [Internet]. 1996;312:1254–9. Available from: <http://www.bmj.com/cgi/doi/10.1136/bmj.312.7041.1254>
53. Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K, et al. Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. *Lancet* (London, England) [Internet]. 1993;341:72–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8093403>
54. Martyn-St James M, Carroll S. Meta-analysis of walking for preservation of bone mineral density in postmenopausal women. *Bone*. 2008;43:521–31.

55. Martyn-St James M, Carroll S. A meta-analysis of impact exercise on postmenopausal bone loss: the case for mixed loading exercise programmes. *Br. J. Sports Med.* 2009;43:898–908.
56. Ehrlich PJ, Lanyon LE. Mechanical strain and bone cell function: A review. *Osteoporos. Int.* [Internet]. 2002;13:688–700. Available from: 10.1007/s001980200095
57. Rubin CT, Sommerfeldt DW, Judex S, Qin YX. Inhibition of osteopenia by low magnitude, high-frequency mechanical stimuli. *Drug Discov. Today.* 2001;6:848–58.
58. Wallace BA, Cumming RG. Systematic review of randomized trials of the effect of exercise on bone mass in pre- and postmenopausal women. *Calcif. Tissue Int.* 2000;67:10–8.
59. Burt LA, Greene DA, Ducher G, Naughton GA. Skeletal adaptations associated with pre-pubertal gymnastics participation as determined by DXA and pQCT: A systematic review and meta-analysis. *J. Sci. Med. Sport* [Internet]. 2013;16:231–9. Available from: <http://dx.doi.org/10.1016/j.jsams.2012.07.006>
60. Ducher G, Tournaire N, Meddahi-Pellé A, Benhamou CL, Courteix D. Short-term and long-term site-specific effects of tennis playing on trabecular and cortical bone at the distal radius. *J. Bone Miner. Metab.* 2006;24:484–90.
61. Ireland A, Maden-Wilkinson T, McPhee J, Cooke K, Narici M, Degens H, et al. Upper limb muscle-bone asymmetries and bone adaptation in elite youth tennis players. *Med. Sci. Sports Exerc.* 2013;45:1749–58.
62. Torvinen S, Kannus P, Sievänen H, Järvinen TAH, Pasanen M, Kontulainen S, et al. Effect of 8-month vertical whole body vibration on bone, muscle performance, and body balance: a randomized controlled study. *J. Bone Miner. Res.* [Internet]. 2003;18:876–84. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12733727>

- 1 63. Kontulainen S, Sievänen H, Kannus P, Pasanen M, Vuori I. Effect of long-term
2 impact-loading on mass, size, and estimated strength of humerus and radius of female
3 racquet-sports players: A peripheral quantitative computed tomography study between
4 young and old starters and controls. *J. Bone Miner. Res.* [Internet]. 2003;18:352–9.
5 Available from: <http://doi.wiley.com/10.1359/jbmr.2003.18.2.352>
- 6 64. Nikander R, Sievänen H, Heinonen A, Daly RM, Uusi-Rasi K, Kannus P. Targeted
7 exercise against osteoporosis: A systematic review and meta-analysis for optimising
8 bone strength throughout life. *BMC Med.* [Internet]. 2010;8:47. Available from:
9 <http://bmcmmedicine.biomedcentral.com/articles/10.1186/1741-7015-8-47>
- 10 65. Zebaze RM, Ghasem-Zadeh A, Bohte A, Iuliano-Burns S, Mirams M, Price RI, et al.
11 Intracortical remodelling and porosity in the distal radius and post-mortem femurs of
12 women: a cross-sectional study. *Lancet* [Internet]. 2010;375:1729–36. Available from:
13 <https://linkinghub.elsevier.com/retrieve/pii/S0140673610603200>
- 14 66. Wolff I, van Croonenborg JJ, Kemper HCG, Kostense PJ, Twisk JWR. The effect of
15 exercise training programs on bone mass: a meta-analysis of published controlled trials
16 in pre- and postmenopausal women. *Osteoporos. Int.* [Internet]. 1999;9:1–12.
17 Available from: <http://link.springer.com/10.1007/s001980050109>
- 18 67. Preisinger E, Alacamlioglu Y, Pils K, Bosina E, Metka M, Schneider B, et al. Exercise
19 therapy for osteoporosis: results of a randomised controlled trial. *Br. J. Sports Med.*
20 [Internet]. 1996;30:209–12. Available from:
21 <http://www.ncbi.nlm.nih.gov/pubmed/8889112>
- 22 68. Ferretti JL, Cointy GR, Capozza RF, Capiglioni R, Chiappe MA. Analysis of
23 biomechanical effects on bone and on the muscle-bone interactions in small animal
24 models. *J. Musculoskelet. Neuronal Interact.* [Internet]. 2001;1:263–74. Available
25 from: <http://www.ncbi.nlm.nih.gov/pubmed/15758500>

- 1 69. Guilhem G, Cornu C, Guével A. Neuromuscular and muscle-tendon system
2 adaptations to isotonic and isokinetic eccentric exercise. *Ann. Phys. Rehabil. Med.*
3 [Internet]. 2010;53:319–41. Available from:
4 <http://linkinghub.elsevier.com/retrieve/pii/S1877065710000898>
- 5 70. Remaud A, Cornu C, Guével A. Neuromuscular adaptations to 8-week strength
6 training: isotonic versus isokinetic mode. *Eur. J. Appl. Physiol.* [Internet].
7 2010;108:59–69. Available from: <http://link.springer.com/10.1007/s00421-009-1164-9>
- 8 71. Bergquist R, Iversen VM, Mork PJ, Fimland MS. Muscle activity in upper-body
9 single-joint resistance exercises with elastic resistance bands vs. free weights. *J. Hum.*
10 *Kinet.* [Internet]. 2018;61:5–13. Available from:
11 <http://content.sciendo.com/view/journals/hukin/61/1/article-p5.xml>
- 12 72. Vainionpää A, Korpelainen R, Leppäluoto J, Jämsä T. Effects of high-impact exercise
13 on bone mineral density: A randomized controlled trial in premenopausal women.
14 *Osteoporos. Int.* 2005;16:191–7.
- 15 73. Tobias JH, Gould V, Brunton L, Deere K, Rittweger J, Lipperts M, et al. Physical
16 activity and bone: May the force be with you. *Front. Endocrinol. (Lausanne).*
17 [Internet]. 2014;5. Available from:
18 <http://journal.frontiersin.org/article/10.3389/fendo.2014.00020/abstract>
- 19 74. Babatunde O, Forsyth JJ, Gidlow CJ. A meta-analysis of brief high-impact exercises
20 for enhancing bone health in premenopausal women. *Osteoporos. Int.* 2012;23:109–19.
- 21 75. Deere K, Sayers A, Rittweger J, Tobias JH. Habitual levels of high, but not moderate
22 or low, impact activity are positively related to hip BMD and geometry: Results from a
23 population-based study of adolescents. *J. Bone Miner. Res.* [Internet]. 2012;27:1887–
24 95. Available from: <http://doi.wiley.com/10.1002/jbmr.1631>
- 25 76. Turner CH. Bone strength: Current concepts. *Ann. N. Y. Acad. Sci.* [Internet].

- 2006;1068:429–46. Available from: <http://doi.wiley.com/10.1196/annals.1346.039>
77. Bettis T, Kim B-J, Hamrick MW. Impact of muscle atrophy on bone metabolism and bone strength: implications for muscle-bone crosstalk with aging and disuse. *Osteoporos. Int.* [Internet]. 2018;29:1713–20. Available from: <http://link.springer.com/10.1007/s00198-018-4570-1>
78. Martyn St-James M, Carroll S. Effects of different impact exercise modalities on bone mineral density in premenopausal women: A meta-analysis. *J. Bone Miner. Metab.* 2010;28:251–67.
79. Babatunde OO, Forsyth JJ, Gidlow CJ. A meta-analysis of brief high-impact exercises for enhancing bone health in premenopausal women. *Osteoporos. Int.* 2012;23:109–19.
80. Allison SJ, Folland JP, Rennie WJ, Summers GD, Brooke-Wavell K. High impact exercise increased femoral neck bone mineral density in older men: a randomised unilateral intervention. *Bone* [Internet]. 2013;53:321–8. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/23291565>

Suppliers: none

Figure legends:

Figure 1: PRISMA Study Flow

Figure 2: Forest plots showing effect of exercises on bone mass of the forearm

a: Forest plot of the overall effect of exercises on bone mass of the forearm

b-d: Subgroup analysis by exercise classifications – resistance exercises high intensity (b); resistance exercises low intensity (c); impact exercises (d)

e: Sensitivity analysis by ROI (33% radius)

Figure 3: Subgroup analysis by populations

- 1 **a:** Postmenopausal women;
- 2 **b:** Premenopausal women
- 3 **c:** Populations with known low bone-health status
- 4 **d:** Populations with mixed or unknown bone-health status (d).

5

6 **Supplementary table/figure/information**

7 Full MEDLINE search strategy

8 **Table S1.** List of eligible/included studies without data in the meta-analysis with reasons

9 Figures S1a and S1b. Summary of risk of bias assessment for all included studies

10

Figure S1: Risk of Bias

- a. Risk of bias for all individual studies included in the analysis.
- b. Summary of risk of bias across all studies included in the analysis.

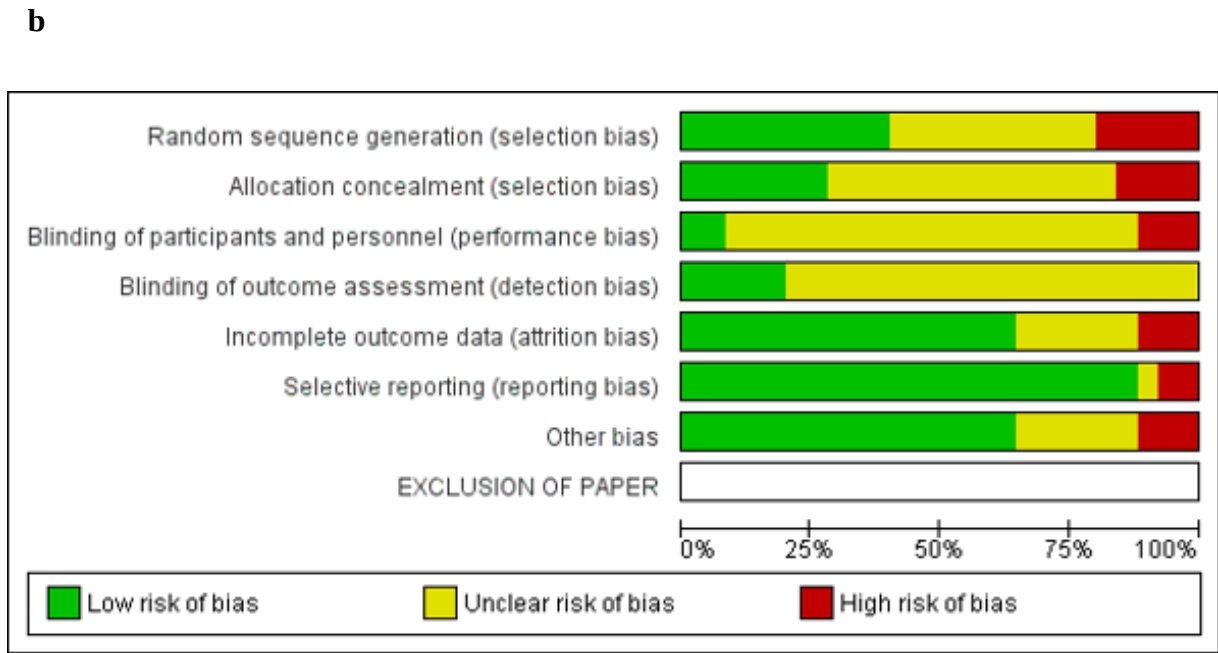


Table 3: Summary of findings and overall grade of evidence

	Evidence base	Magnitude of Effects	Strength of evidence (Grade)	Comments
Exercise (overall)	21 trials n=1505 +5 trials (n=745 not included in meta-analysis)	SMD=1.27, 95% CI=0.66, 1.88 per cent increase in bone mass across participants.	⊕⊕⊕○ Moderate evidence	Beneficial effects. Minimal gains in bone health but uncertainty regarding clinical significance
Resistance exercise with high intensity	15 trials (n=880) +1 trial (n=17 not included in meta-analysis)	SMD=1.00, 95% CI=0.37, 1.62	⊕⊕⊕○ Moderate evidence	~1% increases in bone mass of the wrist and forearm.

Resistance exercise with low intensity	4 trials (n=494) +4 trials (n=728 not included in meta-analysis)	SMD=2.36, 95% CI=0.37, 4.36.	⊕⊕⊕○ Moderate evidence	Significant increases in forearm bone mass.
Impact exercises	2 trials (n=131)	SMD=1.12, 95% CI=-1.27, 3.50.	⊕⊕○○ Low evidence	Beneficial effects on forearm bone mass but not statistically significant. Minimal evidence n trials = 2.
Exercise (Postmenopausal women)	16 trials (n=1246) + trials (n= 308 not included in meta-analysis)	SMD=1.64, 95% CI 0.92, 2.36.	⊕⊕⊕○ Moderate evidence	Beneficial effects demonstrated.

Exercise (Premenopausal women)	5 trials (n=259).	Small effects sizes (SMD=0.25, 95% CI=-0.71, 1.22). Statistically and clinically insignificant	⊕⊕○○ Low evidence	Maybe the type of exercises required for optimal gains in forearm bone mass may be different in this population.
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Conceptualisation: Quality of evidence across studies

⊕⊕⊕⊕ High = Further research is very unlikely to change our confidence in the estimate of effect.

⊕⊕⊕○ Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

⊕⊕○○ Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

⊕○○○ Very low = Any estimate of effect is very uncertain

CI: Confidence interval

SMD: Standard mean difference