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

5

6 J Forsyth, A Evans, K Hind, Z Paskins, O Babatunde.

7

8

9 **Abstract**

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

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

13 **Study selection:** Eligibility included adults undertaking upper-limb exercise interventions
14 [≥ 12 weeks] to improve bone mass.

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

18 **Data synthesis:** Exercise interventions were classified into: 'resistance training' of high or
19 low intensity (RTHI/RTLI, respectively), or 'impact'. Random-effects meta-analysis of the
20 percentage change in forearm bone mass from baseline was conducted. Twenty-six studies
21 were included in the review, of which 21 provided suitable data for meta-analysis.

22 **Methodological quality** ranged from 'low' to 'unclear' risk of bias. Exercise generally led to
23 increases (moderate-quality evidence) in forearm bone mass (standard mean difference
24 [SMD]=1.27, 95% confidence interval [CI]=0.66, 1.88, overall effect Z-value=4.10,
25 $p < 0.001$). RTHI (SMD=1.00, 95% CI=0.37, 1.62, Z-value=3.11, $p = 0.002$), and RTLI

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

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

9

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

11

12 **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
RTL	Resistance training, low intensity
SMD	Standardised mean difference
SPA	Single photon absorptiometry

1

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

18

19 Low bone mass is an important risk factor for fragility fracture. Bone mass is measured as
20 bone mineral content (BMC) or bone mineral density (BMD), which accounts for 60% to
21 70% of variation in bone strength.¹⁰ The lifetime risk of an osteoporotic-related fracture
22 increases 1.5 to 3 times with each SD decrease in BMD;¹¹ therefore, improving bone mass is
23 an important goal of osteoporosis treatment and prevention in clinical practice. Strategies to
24 increase or maintain bone mass can be pharmacological or nonpharmacological. Bone loss is
25 exacerbated by disuse,¹² and conversely, loading of the skeleton promotes bone gain;¹³

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

17

18 Specific objectives of this systematic review were to:

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

23

24

25

1 **Methods**

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

7

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

14

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

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

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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

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

10

11

12 **Results**

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

18

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

24

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

16

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

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

3

4

5 Following classification according to exercise, 16 studies were classified as RTHI,^{26,28–}
6 ^{32,34,35,39,40,45–47,49–51} since they used fixed or free-weight resistance training that induced
7 fatigue within ≤ 12 continuous repetitions and/or a resistance equivalent to $\geq 70\%$ of one
8 repetition maximum (1RM) (Table 2a). Populations (n=897) mostly comprised of
9 postmenopausal women (n=759), who had been previously sedentary. Dose and intensity of
10 exercise were described using sets, repetitions, and repetition maximums (RM) or as a
11 percentage of 1RM. All RTHI studies involved one or more sets of 8 to 12 repetitions,
12 performed to fatigue or at an intensity equivalent to 70% to 90% 1RM, and were progressed
13 to ensure continuous adaptation, often by increasing the load once the required repetitions
14 were achieved. These sets, repetitions, and loads were consistent across studies apart from
15 two that involved a periodised loading pattern, where higher repetitions and lower loads were
16 interleaved with lower repetitions and higher loads.^{39,45} One study failed to provide specific
17 details on sets, repetitions and load.⁴⁷ Studies in the RTHI group were mostly centre-based,
18 using fixed-resistance machines (e.g. lateral pulldown), or free weights (e.g. dumbbell row),
19 and included combinations of biceps curl, triceps extension, triceps push down, shoulder
20 press, bench press, wrist curl, lateral pull down, upright row, front shoulder raise, and row.

21

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

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

11

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

18

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

25

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

5
6 In two RTHI studies,^{29,46} the contralateral limb was used as the control. Participants acted as
7 their own control in one RTLI study.⁴⁴ Five other studies (4 RTHI^{31,38–40} and one RTLI)³⁶
8 involved a comparison group rather than a control group. For those studies with a ‘true’
9 control group, participants in three studies, all RTHI,^{34,49,51} performed ‘sham’ exercise, in the
10 form of stretching and relaxation. One RTHI study failed to describe the control group
11 instruction.⁴⁴ In the remaining studies, including both impact exercise trials, participants were
12 requested to continue with their usual lifestyle.

13
14 Alongside the prescribed exercise, participants in some studies (four RTHI, two RTLI)
15 received calcium supplements.^{26,28,41,43,45,47} Others (three RTHI, two RTLI) received calcium
16 and vitamin D supplements;^{32,36,39,50,51} or dietary advice to take more calcium.³⁰ In one RTHI
17 study, exercise was combined with a daily dose of 0.625 mg conjugated oestrogen.³¹ Across
18 these studies, both the exercise intervention group and the control/comparison group were
19 given the concurrent interventions (i.e. calcium/vitamin D supplements/oestrogen), thus
20 minimising the confounding effect of the intake.

21
22 Fifteen studies measured bone mass using DXA,^{26,28–34,36,37,39,42,45,48,50} six used
23 pQCT,^{35,40,43,44,49,51} and five used SPA.^{27,31,38,41,47} Of the DXA studies, there was variation in
24 the site of measurement, from total forearm bone density.^{32,46} one-third forearm,^{28–30,32,36,50}
25 distal/ultra-distal forearm^{28–30,32–34,36,37,39,42,43,45} and mid-radius.^{26,28,29,34} Accuracy of the

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

4
5 In the RTHI group, two studies that included lower limb interventions, including running and
6 jumping, reported falls during the exercise sessions with 3.6% of exercisers³⁵ and 2.1% of
7 exercisers³⁹ reporting falls during the intervention period. Reported adverse events were
8 mostly a consequence of lower-limb components of the exercise intervention. For example,
9 four participants (12.5%) from the training groups in Karinkanta et al.³⁵ consulted a physician
10 due to lower-limb musculoskeletal injuries. Karinkanta et al also reported 10 patients with
11 ‘overuse’ symptoms at unspecified sites.³⁵ Furthermore, three studies^{29,32,49} reported several
12 minor musculoskeletal complaints, such as muscle soreness and strains. Only one study
13 reported a wrist injury but without further details.²⁸ Other RTHI studies reported no adverse
14 events.^{28,29,31,32,34,35,39,40,45–47,49,50} In the RTLI group, several participants reported mild
15 tendonitis and one participant broke her ankle while walking.²⁹ Other studies, with the
16 exception of Adami et al.,⁴³ failed to report adverse events in relation to exercise. For the
17 impact exercises, mild to moderate soreness during the early intervention period was reported
18 by five participants (21%) in Wang et al.,⁴⁸ but no adverse events were reported by Greenway
19 et al.³⁷

20
21 Twenty-one trials involving 1619 participants provided sufficient data for inclusion in the
22 meta-analysis. All the RTHI trials included in this review were incorporated into the meta-
23 analysis. However, over half of the data for the RTLI exercises could not be pooled
24 statistically. Exercise was generally associated with relative increases in forearm bone mass
25 (SMD=1.27, 95% CI=0.66, 1.88, overall effect Z-value=4.10, p<0.001). Sensitivity analysis

1 for studies which used 33% radius as the region of interest (ROI) (SMD=1.43, 95% CI=0.50,
2 2.36, overall effect Z-value=3.02, $p<0.001$) were consistent with overall effects of exercises
3 at all ROIs. Compared to control/comparators, resistance training, RTHI (SMD=1.00,
4 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
5 value=2.33, $p<0.001$) both led to significant increases in forearm bone mass; however, RTLI
6 exercises led to greater improvements than RTHI. Impact exercises also conferred
7 improvements on bone mass (SMD=1.12, 95% CI=-1.27, 3.50, Z value=0.92, $p=0.36$)
8 compared to control/comparators, but these effects were not statistically significant. Forrest
9 plots of analysis are shown in Figure 2a-e. Postmenopausal women were more likely to
10 benefit from exercise regimes for forearm bone mass (SMD=1.64, 95% CI=0.92, 2.36, Z
11 value=4.46, $p<0.001$) compared to premenopausal women (SMD=0.22, 95% CI=-1.01, 1.45,
12 Z value=0.35, $p=0.72$). Furthermore, subgroup analysis for studies on people with low bone
13 mass/osteoporosis compared to populations with “mixed/unknown” bone-health status at the
14 start of respective trials were performed. Forest plots of sensitivity and further subgroup
15 analyses are presented in Figure 3. A summary of findings of all the included studies with
16 respect to effects of exercise on forearm bone mass is presented in Table 3.

17

18

19 **Discussion**

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

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

4

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

12

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

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

5

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

17

18

19 *Study limitations*

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

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

23

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

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

24

25

1 ***Further research***

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

17

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

1 the lumbar spine and femoral neck of premenopausal women and other populations.^{64,78,79,75,80}
2 Further research into the effect of exercises involving impact or a combination of resistance
3 training with high-impact loading on forearm bone is warranted.
4
5

6 **Conclusions**

7 This is the first systematic review and meta-analysis to examine the effectiveness of exercise
8 interventions for enhancing bone mass of the forearm in adults. There is moderate-quality
9 evidence that resistance training with high or low intensity induces significant effects on
10 forearm bone mass; however, current estimates of effects for most exercise regimes varied in
11 magnitude and were imprecise. Future research into optimal dose and application of exercise
12 interventions for forearm bone mass is needed. In view of the number of possible avenues for
13 further research, future trials will benefit from prior consensus with clinicians, patients and
14 exercise experts in order to prioritise aspects of exercise interventions to be considered for
15 targeting and enhancing forearm bone mass.
16
17

18 **Highlights (optional)**

- 19 • This systematic review and meta-analysis examined the effectiveness of exercise
20 interventions for improving bone mass of the forearm in adults.
- 21 • There is moderate-quality evidence that resistance exercise improves forearm bone mass
22 but low-quality evidence for impact exercise.
- 23 • Available evidence remains equivocal on the optimal dose, intensity and frequency of
24 promising exercise interventions for forearm bone mass.
25

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15

16

17 **Suppliers:** none

18

19 **Figure legends:**

20 **Figure 1:** PRISMA Study Flow

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

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

23 **b-d:** Subgroup analysis by exercise classifications – resistance exercises high intensity (b);

24 resistance exercises low intensity (c); impact exercises (d)

25 **e:** Sensitivity analysis by ROI (33% radius)

26 **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

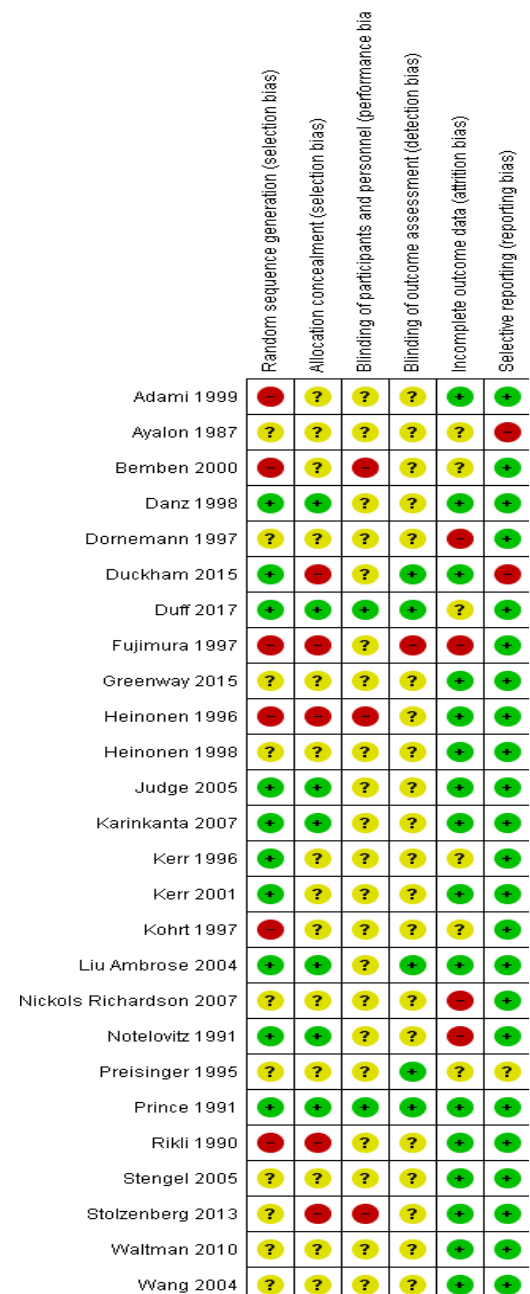
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Figure S1: Risk of Bias

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.

a



b

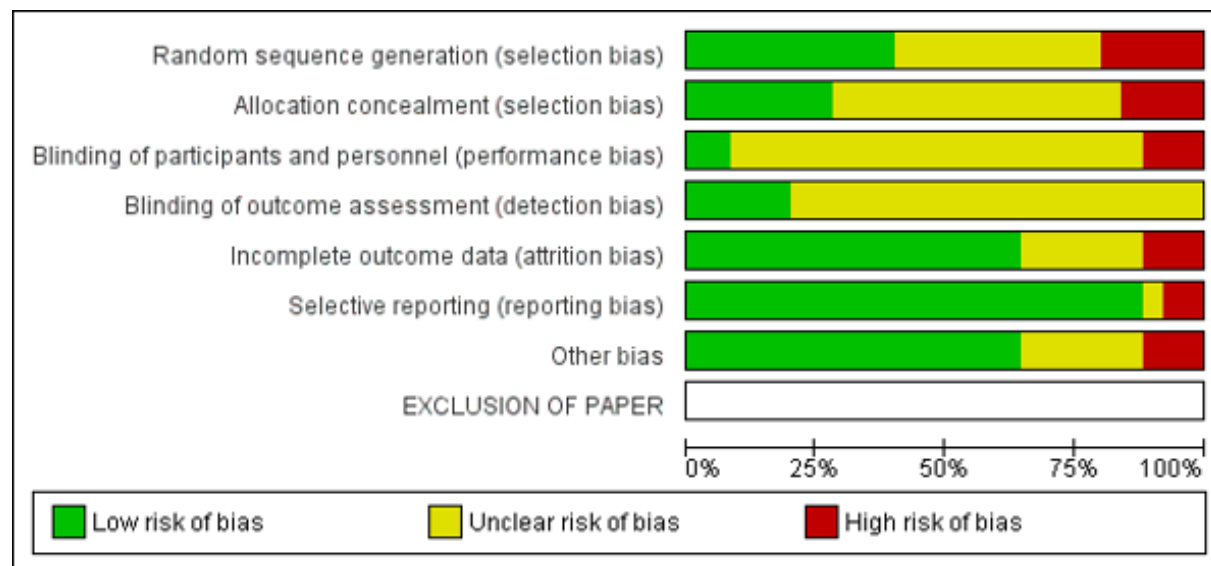


Table 3: Summary of findings and overall grade of evidence

	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