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Title: Non-pharmacological and pharmacological treatments for bone health after stroke: Systematic review with meta-analysis

Abstract

Background: Hemi-osteoporosis is a common secondary complication among stroke survivors. No existing systematic reviews of pharmacological and non-pharmacological agents for post-stroke bone health provided effect size estimate and its precision to guide better clinical practice.

Objectives: To examine the benefits and harms of pharmacological and non-pharmacological agents on different bone health outcomes in post-stroke individuals.

Methods: Eight databases were searched (PubMed, Cochrane library, Scopus, CINAHL Complete, Embase, PEDro, Clinicaltrils.gov and International Clinical Trials Registry Platform). The last search was conducted in June 2023. Any controlled studies that applied physical exercise, supplements, or medications and measured bone-related outcomes in stroke population were included. PEDro and the GRADE approach were used to examine the methodological quality of included articles and levels of evidence for outcomes. Effect sizes were calculated as standardized mean differences (SMD) and risk ratio (RR). Review Manager 5.4 was used for data synthetization.

Results: Twenty-four articles from 21 trials involving 22,500 participants (3,827 in 11 non-pharmacological and 18,673 in 10 pharmacological trials) were included. Eight trials were included in the meta-analysis. The methodological quality of half of the included non-pharmacological studies was either poor or fair, whereas it was good to excellent in eight of ten pharmacological studies. Meta-analysis revealed beneficial effect of exercise on the bone mineral density (BMD) of the paretic hip (SMD: 0.50, 95% CI: 0.16; 0.85; low-quality evidence). The effects of anti-resorptive medications on the BMD of the paretic hip were mixed and thus inconclusive (low-quality evidence). High-quality evidence showed that the administration of the antidepressant increased the risk of fracture (RR: 2.36, 95% CI: 1.64; 3.39).

Conclusion: Exercise under supervision may be beneficial for hip bone health in post-stroke individuals. The effect of anti-resorptive medications on hip BMD is uncertain. The adverse effects of antidepressants on the risk of fracture among post-stroke individuals warrant further attention. Further high-quality studies are required to better understand this issue.

Registration: PROSPERO CRD42022359186

Keywords: Exercise; Medication; bone loss; osteoporosis; stroke; systematic review

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Abbreviations

aBMD	areal BMD
ADL	activities of daily living
ALP	alkaline phosphatase
BAP	bone-specific alkaline phosphatase
BMD	bone mineral density
CI	confidence Interval
CTx	crosslinked C-telopeptide of type I collagen
DXA	dual-energy X-ray absorptiometry
FAME	fitness and mobility exercise
FIM	Functional Independence Measure
GRADE	The Grading of Recommendation, Assessment, Development, and Evaluation
IL-6	interleukin-6
MRI	magnetic resonance imaging
NFT	neuromuscular facilitation training
NTx	crosslinked N-telopeptide of type I collagen
P1NP	procollagen type 1 C-terminal propeptide
PROSPERO	The International Prospective Register of Systematic Reviews
pQCT	peripheral quantitative computed tomography
RR	Risk ratio
RCT	randomized controlled trial
SD	standard deviation
SMD	standardized mean difference
SSRI	selective serotonin reuptake inhibitor
vBMD	volumetric BMD
WBV	whole-body vibration
ICTRP	International Clinical Trials Registry Platform

Introduction

Stroke is a leading cause of long-term disability in adults [1]. Hemi-osteoporosis is a common secondary complication among stroke survivors [2]. Bone mineral density (BMD) of the paretic leg and arm are known to decrease by more than 10% and 20%, respectively, within the first year post-stroke [3]. Decreased BMD, combined with an increased risk of falling, contributes to a highly exaggerated risk of post-stroke fractures (i.e., up to 4-fold more than healthy controls) [4-7]. Hence, the implementation of effective interventions to mitigate post-stroke bone loss is crucial.

Post-stroke bone loss has been associated with disuse of the paretic limb, muscle weakness, and alterations of the mechanical structure and material properties of bone; therefore, exercise interventions may be a promising approach for maintaining or improving post-stroke bone health by modifying these associated factors [8-15]. A systematic review in 2011 [6] investigating the skeletal effects of post-stroke exercise showed that physical activities significantly improved the tibial cortical thickness and femoral neck BMD of the paretic lower limb. However, the review only demonstrated a small treatment effect of exercise on these bone parameters; in addition, the number of studies included in the review was limited and the quality of the evidence was not evaluated systematically. In 2022, Sallehuddin et al. [16] conducted another systematic review of non-pharmacological interventions for post-stroke bone health and found that physical and vibration therapies reduced bone loss in post-stroke individuals. However, it did not provide any information on the effect size estimates and their precision, thus making the interpretation of results difficult.

Meanwhile, the literature on pharmacotherapy for post-stroke osteoporosis spans more than 20 years. A narrative review by Hsieh et al. suggested potential benefits of zoledronate, calcium, and vitamin D for osteoporosis management in individuals with stroke [17]. However, no recent systematic reviews have investigated the effects of pharmacotherapy on bone health in the post-stroke population.

Besides, stroke patients often have other comorbidities, and polypharmacy is

common.[18] Certain pharmacological agents aimed to treat other symptoms may have adverse effects on bone health. A systematic review study with meta-analysis indicated that taking of antidepressant (i.e., selective serotonin reuptake inhibitor, SSRI) can further increase the fracture risk post stroke. [19] On the other hand, a large cohort study indicated that statin use (for hyperlipidemia) was associated with less bone loss post stroke. [20] There is a need to consolidate the evidence on how different types of medications could influence bone health post-stroke.

Taken together, an updated systematic review with meta-analysis is required to interpret the evidence generated in this important area of research. The primary objective of this systematic review was to investigate the effects (benefits and harms) of non-pharmacological and pharmacological agents on the bone outcomes of post-stroke individuals. The secondary objective was to identify the side effects and compliance of these interventions.

Methods

This study was registered on the International Prospective Register of Systematic Reviews (PROSPERO) on September 20, 2022 (registration number: CRD42022359186). The review protocol can be accessed via the following link: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022359186. The reporting of this study follows PRISMA guidelines.

Identification and selection of trials

The PubMed, PEDro, CINAHL Complete, Cochrane Library, Embase, SCOPUS, Clinicaltrils.gov and International Clinical Trials Registry Platform (ICTRP) databases were searched using keywords related to stroke, bone health, physical exercise, pharmacotherapy and supplementation. (Appendix 1) Any interventional studies with comparison control that involved bone-related outcomes in individuals after stroke were included. The study design should be randomized controlled trials (RCT) or quasi-experimental trials. Studies with four

types of comparisons were included: 1) experimental treatment versus no intervention/placebo/usual care; 2) experimental treatment plus other intervention versus the same other intervention only; 3) experimental treatment versus other intervention; and 4) comparisons of different dosages of the experimental treatment. The intervention included all pharmacological or non-pharmacological agents (i.e., physical exercise, supplementation). The outcome measures were standardized or objective scale tests on bone health [i.e., bone variables from dual-energy X-ray absorptiometry (DXA), peripheral quantitative computed tomography (pQCT) scans, serum bone biomarkers and fracture rate]. Books, conference proceedings and non-English publications were excluded. The detailed inclusion and exclusion criteria for article selection are provided in Appendix 2. Two researchers individually screened each article and determined eligibility for inclusion. In the case of a disagreement, the opinion of a third researcher was sought. However, if the disagreement persisted, the senior researcher was consulted for a final decision. Relevant reviews and the reference list of each eligible study were screened to find other potentially relevant studies. Forward reference searching of all relevant studies identified in the above search was conducted using the Science Citation Index (last search was conducted in June 2023).

Assessment of study characteristics and methodological quality

Characteristics of the study populations, outcome measures, and intervention protocols (i.e., dosage of medications and type, frequency, intensity, and duration of exercise) were extracted from each included study. Bone health parameters were classified based on the skeletal site and type of bone structure (e.g., cortical and trabecular), as appropriate. The methodological quality of all studies was rated using the PEDro score from the PEDro website (www.pedro.org.au) . If the score was not available on the website, the article would be independently rated by two experienced researchers. Any discrepancies were discussed until a consensus was reached. PEDro scores of 0–3, 4–5, 6–8, and 9–10 indicated poor, fair, good, and excellent methodological quality, respectively [21].

Data analysis and assessment of strength of evidence

Two researchers independently extracted relevant data from the included studies. One of them used Tabula (v1.2.1) [22] to export tables from PDF to Excel. No discrepancies were found after data extraction and conversion. The standardized mean difference (SMD) was calculated as a summary measure of the treatment effects for interval data. Risk ratio (RR) was used to synthesize the risk of fracture. As suggested by the Cochrane Handbook for Systematic Reviews of Interventions (v6.3), the missing change in standard deviation (SDs) was calculated using the following formula:

$$SD_{E,\ change}=\sqrt{SD_{E,\ baseline}+SD^2_{E,\ final}-(2\times Corr\times SD_{E,\ baseline}\times SD_{E,\ final})}$$

where *Corr* represents the correlation coefficient between pre- and post-intervention outcomes and was set as 0.5.

Meta-analysis was conducted using Review Manager 5.4 software (The Cochrane Collaboration, London, UK) when at least two similar trials tested the same measured construct. Meta-analysis was performed separately for pharmacological and non-pharmacological intervention studies. Considering the variation across study designs, a random-effects model was used for all the meta-analyses. Egger's regression asymmetry test was performed in R software (v4.2.1, R Core Team) to assess publication bias. $p < 0.1$ (two-tailed test) indicated the existence of publication bias if necessary. Forest plots generated by Review Manager were used to display the synthesized results. The heterogeneity across trials was indicated by statistic I^2, with 50% to 90% representing substantial heterogeneity (Cochrane handbook, v6.3).

The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) approach [23] was used to evaluate the quality of evidence for each outcome measure. No observational studies were included in the review. Hence, the initial evidence rating for each outcome was set at "high quality." For each condition specified in Appendix 3, the quality of evidence was downgraded by one level. When a substantial effect size or dose–response association was reported, the quality of evidence was increased by one level.

Results

Flow of studies through the review

The electronic searches generated 7,589 records. After screening and removing duplicates, 35 potentially relevant articles were extracted. Twenty-four eligible papers were identified after full-text screening. These papers were derived from 21 trials because three of the studies generated two papers each (Pang 2005 and Pang 2006 [8, 9]; Pool 2007 and Pool 2009 [24, 25]; Hankey 2020 and Hankey 2021[26, 27]). Four articles were excluded [28-31] because full report was not available despite the effort to contact the authors. Forward reference searching identified two additional retrospective cohort studies [20, 32], which examined the risk of fracture after statin administration post-stroke. They were eventually excluded due to the potential risk of bias arising from their retrospective nature. Finally, 24 papers from 21 trials (eleven non-pharmacological trials, five pharmacological/supplementation trials aiming to improve bone health, 5 pharmacological trials investigating the adverse effects on bone outcomes) involving a total of 22,500 participants (therapeutic effect: 3,827 participants in non-pharmacological and 8,276 in pharmacological/supplementation studies; adverse effect:18,673 participants in pharmacological studies) fulfilled both our inclusion and exclusion criteria (Figure 1).

Characteristics of the included trials

Detailed study characteristics have been summarized in Table 1. The mean age of the participants in individual trials ranged from 57 to 75 years. The disability level of participants varied across studies that investigated non-pharmacological interventions (able to walk with or without aids: three trials; able to stand with or without aids: one trial; motor control deficit: 3 trials; National Institutes of Health Stroke Scale: one trial; Walking speed: one trial; not reported: two trials). Among studies that investigated exercise interventions, five involved people with chronic stroke only (≥ 6 months since onset); two involved a mix of individuals with subacute and chronic stroke (≥ 3 months since onset); and four involved only people with

acute stroke (≤ 5 days since onset). In contrast, all the pharmacological studies except one (≤ 7 month since stroke) involved participants in the acute or subacute stroke stage with a mild-to-severe level of disability.

A wide range of exercise types were adopted in the studies, such as a mix of mobility, balance, and strength training exercises [e.g., the fitness and mobility exercise (FAME) program] (one RCT, one non-randomized controlled study) [8, 9, 33], daily upright bed training (one RCT) [34], exercise on a whole-body vibration (WBV) platform (two RCTs,) [11, 35], progressive body weight-supported treadmill exercise (one non-randomized controlled study) [36], neuromuscular facilitation training (NFT; one non-randomized controlled study), [37] daily hip bridges with conventional training (one non-randomized controlled study) [38] and isotonic finger flexor exercise (one non-randomized controlled study) [39], progressed individualized regularly coached exercise (one RCT) [40] and intermittent pneumatic compression (one RCT) [41]. Four of the eleven non-pharmacological trials were used for meta-analysis.

Five pharmacological studies investigated the therapeutic effect of various drugs and supplements on bone-related outcomes, and all were RCTs. Of these, one study investigated the effect of 2 years of calcitonin supplementation,[42] and another examined the effect of 2 weeks of etidronate administration.[43] The efficacy of modafinil intake for 3 months was investigated in one study.[44] Another tested the effect of one dose of zoledronate in combination with daily calcium and vitamin D supplementation on post-stroke bone health.[25] One large study explore whether the intake of Vitamin B could reduce the fracture risk. [45]

Another five multi-center studies investigated the effect of anti-depressant (n=4) [27, 46-48] or anti-glycemic agents (n=1) [49] on the risk of fracture (Table 1 provides the specific protocols). Four of these five pharmacological trials were included in meta-analysis.

Of the eleven non-pharmacological trials, two used usual care as control, six compared the experimental treatment plus other intervention versus the same other intervention only, one compared the FAME program with an upper limb exercise program which supposedly had no or minimal influence on lower limb bone outcomes, two compared the effects of different dosages of the same intervention method (i.e., different treatment durations of exercise,

different frequencies of whole-body vibration). Of the ten pharmacological trials, one that aimed to improve bone health had a no-intervention control group, whereas the other nine had a placebo control group.

The methodological quality of the trials is shown in Tables 2 and 3. Of the eleven non-pharmacological trials (twelve articles) included in this review, one had excellent and four had good methodological quality, as indicated by their PEDro scores. Of the ten included pharmacological trials, the methodological quality of eight was good-to-excellent and two were fair. (Table 3)

Effects of exercise on bone outcomes

Many of the included studies used either DXA or pQCT to assess the effects of exercise on femur, lumbar spine, tibia, and radius parameters, whereas others used serum bone biomarkers (proteins or derivatives) to assess the effects of exercise on the bone turnover rate. Bone turnover biomarkers included bone formation and resorption biomarkers, which are synthesized and secreted by osteoblasts and osteoclasts during bone remodeling. [50] Fracture risk was used as one of the outcomes in three physiotherapy intervention trials. [33, 40, 41]

Hip areal BMD measured using DXA (g/cm^2)

Three exercise trials used hip areal BMD (aBMD) as the outcome measure. The exercise programs include a 5-month FAME program (RCT, compared with upper limb training) [8], a 6-month progressive treadmill training program (non-RCT, compared with usual activities) [36], and conventional training with NFT (non-RCT ,compared with conventional training alone) [37]. Since in all these three studies, the effect of experimental exercise component on hip BMD can be delineated, meta-analysis was operated. As illustrated in Figure 2A, meta-analysis (three trials, 136 participants) revealed that 5–6 months of exercise significantly mitigated the decline in hip BMD after stroke (SMD: 0.50, 95% confidence interval [CI]: 0.16;

0.85, I^2=0%, low quality evidence). It should be noted that the study by Si et al [37] applied an unusual design which included both animals and human participants. The Pedro score was only 3, indicating poor methodological quality. Thus, caution should be exercised when interpreting the results of this study.

A RCT by Han et al. [34] was not included in the meta-analysis because it compared the efficacies of different exercise durations, and not the exercise intervention with the control condition. Significant effects were only seen in male participants. The study demonstrated that improvement in the paretic femoral neck BMD following daily bedside weight training for 30 min was significantly smaller than that following the same training for 90 min (Hedge's g: 1.16, 95% CI: 0.56; 1.76) among men, with a medium-to-large effect size [34].

Lumbar aBMD measured using DXA (g/cm^2)

As shown in Table 4, only one RCT examined the effect of different dosages of bedside weight training on lumbar aBMD [34]. The results showed that longer training durations per session were more effective in improving the BMD of L1–L4 lumbar vertebra in men (60 min vs. 30 min: Hedge's g: 0.62, 95% CI: 0.05; 1.18, 90 min vs. 30 min: Hedge's g: 1.08, 95% CI: 0.49; 1.68). Among female participants, a stronger treatment effect on the same outcome was observed with the 90-min protocol than with the 30-min protocol (Hedge's g: 0.63, 95% CI: -0.04; 1.30), whereas no difference in outcome was observed between the 30-min and 60-min protocols.

Tibia cortical volumetric BMD (vBMD, g/cm^3), cortical thickness (mm), and total cross-sectional area (*mm^2) measured using pQCT*

Two trials assessed the effects of exercise on cortical vBMD and cortical thickness in post-stroke individuals [9, 36]. One RCT involving the FAME program (compared with upper limb exercises), whereas another was a non-randomized controlled study involving 6 months of treadmill walking training (compared with usual care). Meta-analysis of these two trials (73

participants) showed that exercise had no or a small effect on the cortical BMD of the paretic mid-shaft tibia (SMD: 0.04; 95% CI: -0.42; 0.50; I^2=0%; low quality of evidence) (Figure 2B). The result on the cortical thickness of the mid-shaft paretic tibia was inconclusive because of the wide CI (SMD: 0.43; 95% CI: -0.43; 1.30; I^2=63%; very low quality of evidence) (Figure 2C). The meta-analysis (two trials, 84 participants) also revealed a small or no effect of exercise on the total area of mid-shaft tibia on the paretic side (SMD: 0.018; 95% CI: -0.441; 0.477; I^2=0%; low quality of evidence) (Figure 2D).

Forearm/radius aBMD (DXA, g/cm^2)

Only two non-randomized controlled exercise studies measured the total aBMD of the forearm/radius. Shimizu et al. [39] studied the effect of paretic upper limb resistance training, in addition to physical therapy compared with physical therapy alone, among individuals with chronic stroke, while Si et al. [37] examined the effect of 6 months of NFT in addition to conventional treatment compared with conventional treatment alone in individuals with acute stroke. Shimizu et al. [39] did not find a treatment effect on the forearm BMD (Hedge's g: -0.17, 95% CI: -1.41; 1.08) despite the relatively long training duration (average: 1.8 years). In contrast, Si et al. [37] showed a potential beneficial effect on the radius BMD (Hedge's g: 0.52, 95% CI: -0.03; 1.08). However, both studies had poor methodological quality (PEDro score = 3).

Serum bone biomarkers

Three trials assessed serum bone biomarkers to study the effect of exercise training on post-stroke individuals [11, 35, 37]. Pang et al. [35] (RCT) assessed the serum concentrations of crosslinked C-telopeptide of type I collagen (CTx; a bone resorption marker) and bone-specific alkaline phosphatase (BAP; a bone formation marker) after 8 weeks of WBV with exercise training compared with exercise alone in individuals with chronic stroke. In contrast, Si et al. [37] examined the effect of 6-month NFT (non-RCT), in addition to conventional training compared with the latter training alone, on the total alkaline phosphatase

(a bone formation marker) and serum concentrations of interleukin-6 (IL-6; a bone resorption marker) in individuals with acute stroke.

Meta-analysis of these two studies (134 participants) revealed that the effect of exercise on bone formation (SMD: 0.34; 95% CI: -0.41; 1.10; I^2=78%; low quality evidence) and resorption biomarkers (SMD: -0.91; 95% CI: -2.87; 1.05; I^2=96%; low quality evidence) was inconclusive, as indicated by the wide CIs (Figure 2E and 2F). The heterogeneity between the two studies for serum bone biomarkers was also very large (I^2 > 70%).

A RCT by Yang et al. [11] was not included in the meta-analysis as it compared the effects of similar WBV protocols with different frequencies (20 Hz vs. 30 Hz). The study investigated the influence of 8 weeks of WBV training on the serum concentration of crosslinked N-telopeptide of type I collagen (NTx; a bone resorption marker) [11] and found a significant reduction in NTx concentration following training in both groups ($p < 0.001$), with no between-group difference in the pre- to post-training changes (Hedge's g: 0.13, 95% CI: -0.29; 0.56).

Fracture risk

Three large studies (two RCTs, one non-RCT) studied the effects of different physiotherapy interventions on fracture risk.[33, 40, 41] (Table 4) Dennis et al. [41] compared the immediate effect of 1-month intermittent pneumatic compression and usual thromboprophylactic care with usual care alone (Relative risk or RR: 1.00, 95% CI: 0.25; 3.99). Calugi et al. [33] examined the long-term effect (10 months follow up) after a 2-month adaptive physical activity program (i.e., balance, mobility and stretching) in addition to therapeutic patient education when compared with self-care patient education (RR: 0.24, 95% CI: 0.05; 1.10). Finally, Askim et al. [40] tested the fracture risk after an 18-month progressed individualized coached exercise program when compared with standard care alone (RR: 1.04, 95% CI: 0.46; 2.35). All the three studies reported no between-group difference in fracture risk after the intervention.

Adverse events

Among the non-pharmacological trials, three [34, 37, 38] did not report whether any adverse events occurred, while another three studies reported no adverse events [11, 36, 39]. Five studies reported the following adverse events: small number of falls (four studies) [8, 9, 33, 40, 41] and soreness in the limbs in a small number of participants (two studies) [9, 35]. No significant between-group difference was found regarding these adverse events [8, 9, 33, 35, 40, 41].

Effects of pharmacological agents aimed at improving bone outcomes

Five studies (all are RCTs) investigated whether bone health post-stroke could be improved by pharmacological intervention. All these studies recruited participants in early stages post-stroke (within 7 months).

BMD (DXA, g/cm^2)

Two studies (three papers) examined the effect of anti-resorptive medications on hip BMD in individuals with subacute stroke [24, 25, 43]. Ikai et al. [43] found that a 2-week etidronate administration in addition to 3 months of conventional rehabilitation exercise and dietary calcium had a positive effect on paretic femoral neck BMD, when compared with same treatment without etidronate, in individuals with a poor activities of daily living (ADL) ability (Functional Independence Measure [FIM] ≤ 70) (Hedge's g: 0.83, 95% CI: 0.15; 1.52), but not in those with relatively better ADL ability (FIM ≥ 71) [43]. In another study, Poole et al. [25] showed that adding a single dosage of zoledronate (27 participants) to daily supplements of calcium and vitamin D maintained the hip BMD on the paretic (Hedge's g: 1.53, 95% CI: 0.67; 2.38) and non-paretic side (Hedge's g: 1.24, 95% CI: 0.42 ; 2.06) at 12-month follow-up, when compared with the two supplements alone. When the follow-up interval was halved (6 months), similar benefits on hip BMD was reported by the same researchers on the paretic side (Hedge's g: 1.29, 95% CI: 0.10; 2.49) but not on the non-paretic side (Hedge's g: 0.76, 95%

CI: -0.37; 1.89), based on a smaller sample of participants (n=14).[24]

The effect of a wakefulness promoting drug on whole body BMD has also been explored. Poulsen et al. found that 3-month consumption of modafinil did not bring additional benefits on whole body BMD compared with placebo (Hedge's g: -0.97, 95% CI: -1.97; 0.03).[44]

Serum biochemical markers

One study (RCT) explored the anti-resorptive drug on serum bone turnover markers. Uebelhart et al. found that two-year consumption of salmon calcitonin did not decrease the levels of any of the measured bone resorption markers.[42] The only significant finding was the greater decrease total alkaline phosphatase (a bone formation marker) in the placebo group than the calcitonin group (Hedge's g: 0.89, 95% CI: 0.03; 1.74) (Table 4).

Fracture risk

Two studies examined whether pharmacological intervention can reduce fracture risk in people with stroke. [25,45] Poole et al. did not find any fractures in both the anti-resorptive medication group and the placebo group. [25] Another study by Gommans et al [45] showed that compared with placebo, treatment with B vitamins once daily for 3.4 years did not affect osteoporotic fracture incidence (risk ratio: 0.86, 95% CI: 0.62; 1.18).

Adverse events

The study by Uebelhart et al. [42], which studied the effect of salmon calcitonin, was the only trial that reported no adverse effects. Gommons et al. reported no significant difference in incidence of peripheral neuropathy between the Vitamin B group and placebo control.[45] Two participants (including one who subsequently dropped out) reported stomach discomfort after taking etidronate in the study by Ikai et al. [43]. A single dose of zoledronate infusion led to more cases of acute malaise and pyrexia in the experimental group (three cases) than in the control group (one case), whereas the fall rate was similar in the two groups (10

cases vs. 11 cases). [25] Dizziness (5 cases) and rash (2 cases) were only seen in modafinil group. [44]

Adverse effects of other pharmacological agents on bone outcomes

Fracture risk

High-quality evidence from our meta-analysis (four multi-center RCTs, 6549 participants) indicated that administration of antidepressant (i.e., selective serotonin reuptake inhibitor, SSRI) for 6 months, starting from the acute stroke stage, increased the risk of fracture compared with placebo (risk ratio: 2.36, 95% CI: 1.64; 3.39, I^2=0%: Figure 3).

Viscoli et al. [49] investigated the effects of 4.8 years of use of anti-glycemic agent and found a significant increase in fracture risk in the experimental group than placebo group (risk ratio: 1.53, 95% CI: 1.24; 1.89).

Other adverse events

The consumption of fluoxetine resulted in more cases of hyponatremia (< 130 mmol/L) (11 cases vs. one case) [48] and epileptic seizures (10 cases vs. two cases) [27] in the treatment group than in the control group. The fall rate was slightly higher in the fluoxetine group than the placebo group (4.2% vs. 2.4%, p=0.08; 7.7% vs. 6.0%, p=0.07) in two studies.[26, 47] Compared with the placebo group, more non-cardiovascular death (10 cases vs. three cases) and more urinary/genital symptoms (18 cases vs. seven cases) were reported in the citalopram group.[46]

Compliance

All of exercise studies, except for that conducted by Han et al. [34] ,Tamura et al. [38], and Calugi et al.[33] reported the attrition and training session attendance rates. Approximately half of the trials were with low attrition rate (< 15%) and high attendance rate to training session (> 80%). Of the 60 participants in the study by Pang et al. [9], 24 and eight were excluded

from analysis of the tibial epiphysis and diaphysis bone parameters, respectively, because of poor pQCT image quality arising from movement artifacts. The compliance rate was unspecified in one study for acute stroke [37].

In the pharmacological/supplementation studies, adherence to medication was generally high (≥ 84%) and almost identical in experimental and control group, except in studies by Viscoli et al.[49] Kraglund et al. [46] and Dennis et al. [47], where the adherence rate was about 70%. However, no significant between-group differences in compliance rate were identified in these three studies.

Quality of evidence: GRADE

The number of meta-analyses for non-pharmacological and pharmacological trials was 6 and 1 respectively. The quality of evidence for each analysis, as assessed by GRADE, is shown in Table 5. Overall, for non-pharmacological trials included in meta-analysis, the quality of evidence generated was low for five analyses, and very low for one analysis. For the pharmacological trials that investigated the adverse effects on bone health, high-quality evidence demonstrated increased fracture risk after antidepressant treatment. The quality of evidence for the rest of the analyses was either very low (7 analyses) or low (11 analyses).

Discussion

Our review revealed the use of exercise intervention could protect against hip bone loss after stroke with low-quality evidence. The effects of exercise training on bone health outcomes in other body parts (tibia and radius) and on serum bone turnover biomarkers remain uncertain. Although the treatment efficacy of exercise may be influenced by training duration and sex, the beneficial effect of anti-absorptive medication on paretic hip BMD may be influenced by the ADL level. The consumption of antidepressants can increase the risk of fracture among post-stroke individuals.

Effect of exercise on hip BMD

Our meta-analysis showed that hip BMD was preserved after approximately 5–6 months of exercise training compared with the control condition, with low quality evidence. Pang et al. [8] reported a significant improvement in the paretic femoral neck BMD of individuals with chronic stroke after 5 months of the FAME program. This is consistent with previous findings showing the positive effect of exercise on femoral neck BMD in older men and osteoporotic persons [51, 52]. The combination of aerobic, muscle strengthening, and impact activities can effectively improve bone health as cardiovascular health [53], muscle weakness [54], and lack of weight-bearing [55] are known to be associated with poor bone health outcomes in people with stroke. In individuals with acute stroke, Si et al. [37] showed that daily NFT, in addition to conventional weight-bearing training, for 6 months improved femoral neck BMD. The benefits of NFT for hip bone health may be attributable to active muscle contractions facilitated by the sensorimotor stimulation, paretic limb weight-bearing, and reflex inhibition. These approaches may be useful in inducing muscle activity during the acute and subacute stroke stages, when active and voluntary muscle activities are most likely to be impaired.

Of the three exercise studies included in the meta-analysis, the study by Pang and Lau [36] showed no significant improvement in total hip BMD after a 6-month treadmill exercise program. The lack of significant findings may be due to the small sample size (n = 10 in each group), rendering the study underpowered to detect significant changes in bone health outcomes after training. In addition, the participants in Pang and Lau had more chronic stroke (post-stroke duration: 7 to 9 years) when compared with in Si et al (3 days) [37]and Pang et al (5 years) [8]. This may lead to more modest changes after exercise in the former study. The low-quality evidence level was caused by imprecision from insufficient sample size and potential risk of bias from the included non-RCTs. More robust RCTs are still required to further verify this positive evidence.

Effects of exercise on tibia bone health outcomes

Our meta-analysis showed that the effect of exercise on the cortical thickness of the mid-shaft tibia was inconclusive. The evidence was of very low quality because of the small sample size and risk of bias of the two included studies. Pang and Lau [9] demonstrated a large effect size (Hedge's g: 0.96) of a 6-month treadmill training program on the cortical thickness of the paretic side tibia. This was in line with other studies suggesting that enhanced endocortical surface thickness and/or BMD after mechanical loading could underlie exercise-induced skeletal benefits [52, 56]. Progressive treadmill walking exercises may improve bone health by providing mechanical stimulation and enhancing cardiopulmonary health [57, 58]. In contrast, a study involving a 5-month integrated exercise program reported no effects on tibia bone health [9]. This negative finding may have arisen due to the large variation (SD) in the results. Thus, a future study targeting a population is warranted.

Effects of exercise on forearm/radius bone health outcomes

Si et al. [37] found that NFT during the first half-year after stroke decreased bone loss (aBMD) in the radius with a medium effect size. A meta-analysis of two studies also showed a beneficial effect of upper extremity exercise on the cortical area of the radial shaft in post-menopausal women [59]. In contrast, a study by Shimizu et al. [39] involving 10 post-stroke individuals found no protective effects of progressive isotonic finger flexor exercises on forearm aBMD in individuals with chronic stroke. This discordance may be attributable to differences in sample size and participants' stroke recovery. In particular, the study by Shimizu et al. [39] lacked precision and power because of the small sample size of 10. Moreover, potential for the functional recovery required to promote bone health is less in individuals with chronic stroke [39] than in those with acute stroke [37]. Thus, whether exercise has beneficial effects on radius bone loss in individuals with chronic stroke remains uncertain and should be investigated in a study with a sufficiently large sample size.

Effects of exercise on serum bone biomarkers

Our meta-analysis found that the effects of exercise on bone formation and resorption biomarkers were inconclusive. Si et al. [37] found significantly more decline in the level of interleukin-6 [IL-6] (a bone resorption biomarker) and more increase in the level of alkaline phosphatase (ALP, a bone formation biomarker) after an additional NFT exercise, compared with 6 months of conventional training alone. In contrast, Pang et al. [35] found no significant changes in bone formation and resorption markers following an 8-week WBV program.

The discrepancies between the findings of these two studies might be attributable to differences in treatment durations (6 months in Si et al. vs 8 weeks in Pang et al.) and stroke chronicity of the participants (less than 3 days in Si et al. vs 5 years in Pang et al.). A narrative review of the application of serum biomarkers for osteoporosis management reported that biomarker concentrations can be used to reflect the treatment effectiveness after 3–6 months of training [60]. This indicates that the treatment duration used in the study by Pang et al. (8 weeks) may be insufficient, especially for participants with chronic stroke. The treatment frequency and duration per session in the study by Pang et al. (3 times/week, 15 min/time) were also much less than those in the study by Si et al. (almost daily, 1–2 times/day, 60–90 min/time). In addition, the two studies evaluated different serum bone biomarkers (Pang et al.: BAP and CTx; Si et al.: ALP and IL-6). A systematic review suggested that BAP could be a superior bone formation biomarker to ALP as the latter was not specific to bone turnover, despite having been widely used for this purpose [61]. Another recent review [50] compared different bone biomarkers based on applicability in four aspects—diagnosis, progression, monitoring, and predictive value —and found that the two most specific and sensitive biomarkers for osteoporosis pharmacotherapy were CTx-1 (for bone resorption) and procollagen type 1 C-terminal propeptide (P1NP; for bone formation) [50, 61, 62]. Further research is required to evaluate the effects of different exercise protocols on bone biomarkers in post-stroke individuals.

Effects of pharmacological agents on hip BMD

The beneficial effects of pharmacotherapy for osteoporosis have long been established in non-post-stroke populations such as post-menopausal women [63]. However, only two studies have investigated the efficacy of anti-resorptive agents (etidronate and zoledronate) on proximal femur BMD in individuals with acute stroke [25,43]. While a single dose of zoledronate was reported to have some benefits [25], etidronate only induced significant treatment effect in individuals with low ability to perform ADL [43]. This finding indicates the importance of proper screening to identify individuals who may benefit more from pharmacotherapy. In summary, the results on anti-resorptive agents are mixed and further research is warranted.

Side effects of pharmacological agents on fracture risk

Furthermore, the consumption of antidepressants (i.e., SSRI) was found to increase the risk of fracture by two to three times, as revealed in another meta-analysis which focused the fracture risk among stroke people treated with SSRIs.[19] Wadhwa et al. [64] suggested that reduction of osteoblast proliferation by gut-derived SSRIs maybe a mechanism underlying bone loss. Mixed results were found regarding the relationship between the consumption of antidepressants and BMD change in post-menopausal women [65-67]. Studies by Rauma et al. and Diem et al. [66, 67] demonstrated that SSRIs increased bone loss in post-menopausal women, but another study by Diem [65] showed no association between the use of SSRIs and an increased rate of bone loss. This discrepancy is mostly attributable to differences in the age and post-menopausal duration of the participants. Diem [65] investigated middle-aged women (mean age: 49 years, 24.1% post-menopausal), whereas the mean ages of the women in the other two trials were 63 [67] and 79 years (menopause age: 49 years) [66], respectively. This indicates that SSRIs may be more detrimental to bone health in women of advanced age and with a relatively long post-menopausal period. In summary, future study should investigate whether age would mediate the influence of SSRIs on fracture risk in the stroke population.

Potential Influential factors, clinical and research implications

Among the various analyses done, it was supported that the use of exercise may help maintain hip BMD among people with stroke (low evidence). Moreover, there was substantial diversity in the exercise protocol across the studies involved in the meta-analysis. Therefore, future research is needed to identify the optimal exercise protocol with robust methodology. This review has shed some light into the potential factors that may influence treatment outcomes, which may need further exploration.

Exercise protocol is the first potential influential factor. Three exercise programs showed positive effects to bone health [8, 36, 37]. All these programs included muscle strengthening or weight-bearing exercises. In contrast, the WBV training program had no beneficial effects on bone turnover biomarkers [35]. This negative finding could be partly attributable to the type of exercise implemented; as the WBV program mainly involved static posture maintenance with vibratory stimulation, the exercise intensity was low and engendered only a moderate cardiovascular training effect and inadequate active muscle work. Another factor may be the shorter exercise training duration of the WBV program (15 min per session, 2 months) than of the three beneficial exercise programs reported above (60 min per session, 5–6 months). Indeed, the study by Han et al. [34] showed that a longer duration of weight-bearing exercises (60–90 min per day) led to higher gains in the femoral neck and lumbar spine BMD than 30 min of training per day. However, as multiple exercise parameters differed across the different trials, it was impossible to evaluate the impact of each of these parameters on the overall treatment effect.

In addition, several participant characteristics (e.g., sex, stroke chronicity, ADL function) could be potential factors that influence treatment success as well. Our results revealed a larger treatment effect on the hip BMD, radius BMD, and serum biomarkers in individuals with acute stroke [37] than in those with chronic stroke [8, 35, 36, 39]. Moreover, Han et al. [34] demonstrated that women required longer training durations than men to show improvements

in bone outcomes. Ikai et al (34) showed that those with poor ADL ability had better outcome in hip BMD after exercise training but the FIM cutoff score used to define poor ADL ability (FIM ≤ 70) seemed arbitrary, as a FIM score of <72 was used in previous research to indicate severe deficit in ADL function [68]. Nevertheless, a relatively small number of studies made it unfeasible to perform sensitivity analyses to identify the determinants of treatment success (e.g., exercise parameters and participant characteristics) and the dose–response relationship. Thus, to identify optimal exercise training protocols for participants with different gender and stroke chronicity, well-controlled studies that clearly delineate the effects of different exercise parameters are warranted.

The prescription of antidepressant to stroke population need caution for its side effects of increased fracture risk. For post-stroke people who are on SSRI, fall and fracture risk screening is highly recommended. For those with high fracture risk and high fall risk, intervention (e.g., balance training, fall prevention education) to protect bone health and prevent falls is urgently recommended. Or choosing an alternative antidepressant may be another option.

Limitations of reviewed studies

These included articles have several limitations. The methodological quality of half of the included non-pharmacological studies was either poor or fair. The meta-analyses involved a relatively small number of trials, and some included non-RCTs. However, potential risk of bias stemming from non-randomization and imprecision were considered when using the GRADE evaluation tool to assess the quality of evidence for each outcome. Advanced bone imaging techniques, such as high-resolution pQCT or magnetic resonance imaging (MRI), or highly sensitive and specific serum bone biomarkers, such as P1NP and CTx-1, were not commonly used in the reviewed studies. Furthermore, none of the studies investigated the retention effects of exercise. And the effect of medication on the bone turnover rate is also understudied. Little is understood about the site-specific effect of exercise on trabecular bone.

Taken together, more RCTs including pharmacological trials to protect bone health with sufficient samples and long-term follow-ups are needed. As DXA-measured BMD alone may have its limitations [52], employing a combination of measurements such as serum bone markers, pQCT, DXA-based hip structural analysis, and MRI which measures both cortical and trabecular bone is recommended.

Limitations of this systematic review

The overall number of participants in the meta-analysis was relatively small, which may have reduced the precision of analysis. The limited number of studies make it infeasible to assess publication bias. Interpreting the result of those meta-analyses that involve different study design (RCT and non-RCT) and different exercise protocols requires caution. These factors may partially explain the substantial heterogeneity in some meta-analyses ($I^2 \geq 50\%$). Nevertheless, the problems with risk of bias, inconsistency and imprecision were considered when rating the quality of evidence using GRADE.

Conclusion

In conclusion, supervised exercise may be an effective way to improve hip bone health for post-stroke individuals. The evidence for integrated exercise post-stroke to maintain or improve bone health of hip, tibia or radius is of low or very low quality. The therapeutic effect of anti-resorptive medications on hip BMD is uncertain. The consumption of antidepressants (i.e., SSRIs) can have adverse effects on the bone health of post-stroke individuals.

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Figure legend

Figure 1. Flow of studies through the review process

Figure 2. Meta-analysis: Effect of exercise on bone parameters on the paretic side. A) Hip: Total BMD (g/cm2, DXA); B): Tibia (mid-shaft): Cortical BMD (g/cm3, pQCT); C): Tibia (mid-shaft): Cortical thickness (mm, pQCT); D): Tibia (mid-shaft): Total cross-sectional area (mm2, pQCT); E): Bone formation biomarker (serum total alkaline phosphatase & BAP); F): Bone absorption biomarker (serum).

Figure 3. Meta-analysis: Side effect of pharmacological agents on fracture risk

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Table 1: Table summarizing study characteristics

Study (year) Quality	Key participant characteristics mean (SD)	Intervention protocol	Outcome measure
Non-pharmacological interventions that are aimed to improve bone health			
Yang 2021 [11] PEDro score =9 (excellent) RCT	20Hz: n=42 (13 females), age= 60.4 ± 5.9 30Hz: n=42 (17 females), age= 59.0 ± 7.0 **Years since stroke onset**: 4.6 (3.5) **Impairment/disability level:** FMA-LL motor score: 24.0 (3.5) Able to stand for at least 1 min with hand support	**Low frequency (20Hz) group:** Whole-body vibration training on Jet-Vibe System. Synchronous vertical vibrations of 20Hz: 1-min bouts, with 1-min rest between bouts, 12 bouts/session **High frequency (30Hz) group:** Whole-body vibration training on Jet-Vibe System Synchronous vertical vibrations of 30Hz: 1-min bouts, with 1-min rest between bouts, 8 bouts/session **Frequency** in both groups**:** 3 days/week for 8 weeks	Serum cross-linked N-telopeptides of type I collagen (NTx) No adverse events occurred.
Askim 2018 [40] PEDro score =7 (good) RCT	EXP: n=186 (82 female), age= 71.7 (11.9) CON: n=194(67 female), age= 72.3 (11.3) Days since stroke onset: EXP: 111.3 (24.5) CON: 112.0 (17.2) Impairment/disability level: EXP: NIHSS=1.5 (2.3) CON: NIHSS=1.6 (2.5)	**Intervention group:** Standard care plus progressed individualized regular coaching on physical activity and exercise every month for 18 consecutive months: 45 to 60 minutes and include 2 to 3 periods of vigorous activity once a week while the physical activity needed to last 30 minutes 7 days a week. **Control group:** standard care alone	Fractures **Adverse Events:** There were 39% more hospital admissions because of vascular events in the CON (EXP=17, CON=28; p=0.11). 3 falls in EXP and 4 falls in CON.

Han 2017 [34] PEDro score =4 (fair) RCT	Total number: n= 129 (54 females) **Age**: 66.6 (/) **M30**: n=25 males, age=65.4±5.72 **M60**: n=25 males, age=62.7±4.25 **M90:** n=25 males, age=67.9±5.68 **F30:** n=18 females, age=66.3±4.82 **F60:** n=18 females, age=70.2±7.69 **F90:** n=18 females, age=68.8±6.27 **Months since stroke onset**: 5.1 **Impairment/disability leve**l: Able to stand with dynamic standing bed	Type of exercise: Daily upright bed weight training for different durations **M30, F30 groups:** 30 minutes **M60, F60 groups:** 60 minutes (with an interval of 6h) **M90, F90 groups:** 90 minutes (with an interval of 3h) In addition to basic treatment: i) lifestyle adjustment ii) basic dietary supplements for bone health **Frequency:** 5 days/week, 3 months	BMD at the anteroposterior lumbar spine (L1-L4) and ipsilateral femoral neck Adverse events not reported.
Calugi 2016 [33] PEDro score =5 (fair)	EXP: n=126 (41 female), age=71.8±10.5 CON: n=103(41 female), age=70.1±10.7 Days since stroke onset: EXP: 287.3±126.8 CON:194.1±128.2 Impairment/disability level (6-Minute Timed Walk): EXP: 235.6±115.3 CON: 166.1±92.2	**Intervention group:** 16 biweekly sessions of adaptive physical activity (APA: mobility, balance and stretching) + 3 therapeutic interactive patient education (TPE) sessions **Control group:** non-structured self-care education (recommendations provided in the letter of discharge and two follow-up visits in a year)	Baseline and 10 months after intervention Fracture **Adverse events:** 23 falls in EXP and 33 falls in CON.
Si 2016 [37] PEDro score =3 (Poor)	Total number: n=26 (30 females) Age:45–75 Time since stroke onset: ≤3 days Impairment/disability level: **EXP**: FMA-UL=8.84(4.36), FMA-LL=13.52 (6.39) **CON**: FMA-UL=8.97(4.57), FMA-LL=13.46 (6.53)	**Intervention group:** conventional treatment + neuromuscular facilitation technique (NFT). NFT included the Bobath, Brunnstrom and Rood techniques. **Control group:** conventional treatment **Frequency** in both groups: 60–90 minutes every time, 1–2 times a day, for 5–6 days a week,6 months	DXA: radius & femur neck BMD, serum Osteocalcin, IL-6 and leptin, serum alkaline phosphatase (ALP) Adverse events not reported.
Pang, Lau & Yip, 2013 [35] PEDro score =8 (good) RCT	EXP: n=41 (15 females), age= 57.3 (11.3) CON: n=41 (9 females), age= 57.4 (11.1) **Years since stroke onset**: 4.95 **Impairment/disability leve**l: Abbreviated Mental Test score >= 6; able to stand 1.5 minutes with or without aids **Functional ambulatory category out of**	**Intervention group:** o Exercise training with vertical WBV stimulation, with progression on WBV intensity and duration o Exercise protocol on the WBV platform: Side to side weight shift/Semi squat/Forward and backward weight shift/Forward lunge/Standing on one	Bone turnover markers(ng/ml): Serum cross-linked C-telopeptides of type I collagen (CTx); Serum level of bone-specific alkaline phosphatase (BAP) **Adverse events:** No major adverse events were reported by the

	5 EXP: 5;5-5; CON: 5;5-5 **CMSA leg/foot/arm/hand score out of 7** EXP:4(0)/3(1)/3(2)/3(3) CON:4(0)/3(2)/3(2)/3(3)	leg/Deep squat **Control group:** The same exercises as the experimental group on the WBV platform without WBV **Frequency** in both groups**:** maximum of 15 minutes, 3 days per week, 8 weeks	participants, although three felt mild dizziness during first few sessions of the WBV, and four (two from the WBV group) experienced lower limb soreness and fatigue which lessened within a few weeks.
Dennis 2013 [41] PEDro score = 7 (good) RCT	EXP: n=1438(695 female),age=74.2 (12.3) CON:n=1438(688 female),age=74.9 (11.9) Time since stroke onset: within 3 days Impairment/disability level: (Able to lift both arms off bed) EXP: 499 (35%) CON: 502 (35%)	**Intervention group:** Usual care plus intermittent pneumatic compression: day and night (except during washing, physiotherapy, or screening compression duplex ultrasound) for about 30 days **Control group:** usual thromboprophylactic care alone	Baseline, 30 days Fracture **Adverse events:** Falls with injury [EXP: 33 (2.3%); CON: 24 (1.7%), p=0.22]
Tamura 2011 [38] PEDro score =3 (Poor)	**EXP**: n=15; Age: 67.2 ± 11.7; Time since stroke onset: 3–5 days; Impairment/disability level: Brunnstrom stage (lower extremities), Stage IV–VI/Stage I–III: 6/9 **CON**: n=12; Age:64.5 ± 11.3; Time since stroke onset:3–5 days; Impairment/disability level: Brunnstrom stage (lower extremities), Stage IV–VI/Stage I–III: 8/4	**Intervention group:** daily hip bridges + standard rehabilitation **Control group:** standard rehabilitation **Frequency** in both groups: 20 minutes/day, one week	Adverse events not reported.
Pang & Lau, 2010 [36] PEDro scode =5 (fair)	EXP: n=10 (3 females), age= 64.6 (7.2) CON: n=11 (4 females), age= 64.5(6.2) **Years since stroke onset**: EXP: 7.3 (4.2); CON: 9.3 (3.2) **Impairment/disability leve**l: CMSA Leg Score (1-7) EXP: 4.3 (0.9); CON: 4.3 (1.3) CMSA Foot Score EXP: 3.2 (1.5); CON: 2.7 (1.3)	**Exercise group:** 6-month progressive treadmill exercise intervention program with bodyweight supported (BWS). o Initial training speed: individualized comfortable speed. o With intermittent 2-minute rest periods, warm-up and cool-down exercises **Frequency:** 1-hour x 2 sessions/week, 52 sessions, 6 months **Control group:**	Hip BMD (using DXA) Tibial BMD and geometry No adverse events occurred.

		usual activities (eg, leisure walking, light household tasks)	
Pang 2006 [9] PEDro score =6 (good) RCT	4% site: EXP: n=18 (9 female), age= 63.9±7.0 CON: n=18(6 female), age= 63.7±7.6 4% site: EXP: n=26 (11 female), age= 65.2±8.8 CON: n=26 (10 female), age= 64.7±8.5 **Years since stroke onset**: 5.2 (5.0) **Impairment/ disability level**: American Heart Association Functional classification (I/II/III/IV/V) 4% site: EXP: 2/12/4/0/0 CON: 1/12/5/0/0 50% site: EXP : 3/16/7/0/0 CON: 1/15/8/2/0	**Exercise group:** Fitness and mobility exercise (FAME) program designed to improve cardiorespiratory fitness, mobility, leg muscle strength, balance, and hip BMD **Control group:** Seated upper extremity exercise program include upper extremity muscle strengthening exercises, passive of self-assisted range of motion exercises, and functional training **Frequency** in both groups**:** 1 hour per session, 3 sessions/week for 19 weeks	Total bone area; Trabecular bone area; Trabecular BMD; Trabecular BMC; Cortical bone area; Cortical BMC; Cortical BMD; Cortical thickness; Polar stress-strain index (p-SSI) **Adverse events:** Five falls (three falls occurred with the participant still holding onto a support) happened in EXP and 1 fall in CON.(p=0.08)
Pang 2005 [8] PEDro score =8 (good) RCT	EXP: n=32 (13 female), age= 65.8(9.1) CON: n=31(13 female), age= 64.7(8.4) Years since stroke onset: 5.15(4.25) **Impairment/disability level**: American Heart Association Stroke Functional Classification: I/II/III/IV/V EXP: 5/17/9/1/0 CON: 2/19/8/2/0	**Exercise group:** Fitness and mobility exercise (FAME) program designed to improve cardiorespiratory fitness, mobility, leg muscle strength, balance, and hip BMD (Appendix A) **Control group:** Seated upper extremity program **Frequency** in both groups: 1 hour per session, 3 sessions/week for 19 weeks	femoral neck BMD (using DXA) **Adverse events:** Five falls (three falls occurred with the participant still holding onto a support) happened in EXP and 1 fall in CON. (p=0.08)
Shimizu, Ishizaki & Nakamura, 2002 [39] PEDro score =3 (poor)	EXP: n=5 (1 female), age=62.6 (9.2) CON: n=5 (1 female), age=63.0 (8.1) **Years since stroke onset**: EXP: 4.6 (3.8) CON: 4.4 (5.4) **Impairment/disability leve**l: Unspecified	**Exercise group:** Type of exercise: Ball squeezing exercise in sitting, elbow flexed, arm resting on the armrest. **Frequency:** 10 times x 2 sets/day; 3 times/week or more In addition to standard Physical therapy. **Control group:** Standard Physical therapy only.	Bilateral upper extremity: total bone area, BMC, and BMD (DXA) No adverse events occurred.
Pharmacological/supplementation intervention aimed to improve bone health			
Poulsen 2015 [44]	**EXP**: n=7; Age: 69 (62–79); Days since stroke/TIA onset: 8 (6–11); Disability level: MRS median (IQR): 3(2–	**EXP:** 400-mg modafinil or placebo in 100-mg tablets (200 mg if the patient was ≥65 years) **CON:** placebo	Bone mineral density (DXA) **Adverse events:**

PEDro score = 6 (good) RCT	4) **CON**: n=11; Age: 71 (65–82); Days since stroke/TIA onset: 9 (6–14); Disability level: MRS median (IQR): 3 (2–4)	**Frequency** in both groups: target dose, mg daily for 3 months	Dizziness (5 EXP, 0 CON) and rash (2 EXP, 0 CON)
Gommans 2013 [45] PEDro score =9 (excellent) RCT	Age: 62.6 ± 12.5. Stroke or TIA **EXP**: n=4089; Years since stroke/TIA onset: with within 7 months; Impairment/disability level: independent walking **CON**: n=4075; Years since stroke/TIA onset: within 7 months ; Impairment/disability level: independent walking	**EXP**: one tablet daily of B-vitamins (folic acid 2 mg, vitamin B6 25 mg, vitamin B12 500 µg **CON**: one tablet daily of placebo **Frequency** in both groups: 2.8 years	Fracture risk **Adverse events:** There were no unexpected adverse events. Peripheral neuropathy were observed in 5 from EXP group and 9 from CON group (p=0.30)
Poole 2007 [25] PEDro score =8 (Good) RCT	**N=6 females** **EXP**: n=14; Age: 66.9 (11.7); Days since stroke onset: within 35 days of stroke; Impairment level: SSS=27.4 (6.6) **CON**: n=13; Age:72.9 (10.4); Days since stroke onset: within 35 days of stroke; Impairment level: SSS= 24.7 (7.5)	**Intervention group:** single dose of zoledronate 4mg with daily calcium (1g) and vitamin D (800 IU) **Control group:** placebo infusion in 50-mL coded sachets with daily calcium (1g) and vitamin D (800 IU) 12-month follow-up	Hip BMD (DXA), Barthel index, Scandinavian Stroke Scale, FAC **Adverse events:** "Acute phase" symptoms of post infusion malaise and pyrexia were observed (3 EXP, 1 CON) and falls (10 EXP, 11 CON).
Pool 2009 [24] PEDro score =8 (Good) RCT	**N=3 females** **EXP**: n=5; Age: 67.2 (52.8, 81.6); Days since stroke onset: within 35 days of stroke; Impairment level: SSS=29 (21, 37) **CON**: n=9; Age: 72.7 (64.3, 81.0); Days since stroke onset: within 35 days of stroke; Impairment level: SSS= 28 (22, 39)	**Intervention group:** single dose of zoledronate 4mg with daily calcium (1g) and vitamin D (800 IU) **Control group:** placebo infusion in 50-mL coded sachets with daily calcium (1g) and vitamin D (800 IU) 6-month follow-up	Hip BMD (DXA) One measurement for static, endocortical and dynamic histomorphometry from a single trans-iliac bone biopsy. Adverse events were not reported but it was the same study as Poole 2007 above.
Ikai 2001 [43] PEDro score =4 (Fair) RCT	**All female** **EXP**: n=40; Age: 66.0 (8.1); Months since stroke onset: 2.7 (1.4) Impairment/Disability level: Brunnstrom stage (lower limb):3.6 (1.3) **CON**: n=41; Age: 67.0 (8.9); Months	**Intervention group:** a dose of 200 or 400 mg/ day of etidronate for a 2-wk period +3 months rehabilitation exercise (PT+OT) + dietary calcium. **Control group:** Rehabilitation exercise (PT+OT) + dietary calcium	**BMD**: lumbar spine and both sides of the femoral neck (DXA), FIM **Bone formation markers**: Serum levels of alkaline phosphatase (ALP) and osteocalcin were measured as markers of bone formation, **Bone absorption markers**: urinary pyridinoline, urinary

	since stroke onset: 2.6 (1.2) Impairment/disability level: Brunnstrom stage (lower limb):3.4 (1.4)	**Frequency**: rehabilitation exercise 5 days a week, in 40min sessions, 3 months	deoxypyridinoline, and serum crosslinked carboxy-terminal telopeptide of type 1 collagen (ICTP). Low ADL: FIM ⩽70 points **Adverse events:** 2 reported stomach discomfort (1 dropout)
Uebelhart 1999 [42] PEDro score =6 (Fair) RCT	**N**=34 (13 female) **EXP**: n=18; Age: 62(10); Days since stroke onset: 23 (1) **CON**: n=16; Age: 52 (15); Days since stroke onset: 22 (8) Impairment/disability level: unspecified	**Intervention group:** 1 0 0 IU of salmon calcitonin as a nasal spray +1 g daily oral supplementation of calcium + Bobath rehabilitation. **Control group:** placebo nasal spray+1 g daily oral supplementation of calcium+ Bobath rehabilitation. **Frequency**: twice a day for two years. Two stages: Hospital (4-6 months), Discharged (2 years)	**Serum biochemical markers**: total alkaline phosphatase (TAP), osteocalcin (OC), carboxy-terminal extension peptide of type I procollagen (PICP), cross-linked carboxy-terminal telopeptide of type I collagen (ICTP), amino-terminal extension peptide of type III procollagen (PIIINP) **Urinary biomarkers**: calcium/creatinine (Ca/cr) ratio, hydroxyproline/creatinine (HOP/cr) ratio. **Adverse events:** No abnormal biological profile was noticed and none of the participants presented with any fracture.
Adverse effects of other pharmacological/supplementation interventions on bone health			
Hankey 2020 [27] & Hankey 2021 [26] PEDro score =10 (excellent) RCT	**EXP**: n=642 (female=36%), Age= 63.5 (12.5), Days since stroke onset= 6.1 (3), Impairment/disability level: NIHSS Median (IQR)= 6.0 (3.0–9.0) **CON**: n=638 (female=38%), Age = 64.6 (12.2), Days since stroke onset= 6.3 (3), Impairment/disability level: NIHSS Median (IQR)=6.0 (3.0–9.0)	**Intervention group:** oral fluoxetine 20 mg **Control group:** placebo **Frequency** in both groups: once daily for 6 months	Measured at 6-month post treatment: Fractures, mRS, mood (Patient Health Questionnaire 9 score), and health-related quality of life using the EQ5D-5L **Adverse events:** Falls with injury [EXP: 27 (4.2%); CON: 15 (2.4%), p=0.08]
Lundström 2020 [48] PEDro score =10 (excellent) RCT	**EXP**: n=750 (female=38%), Age=70.6 (11.3), Days since stroke onset (Median)=5.0 (4.0–8.0), Impairment/disability level: NIHSS Median (IQR)= 3.0 (2.0–6.0) **CON**: n=750 (female=38%), Age =71.0 (10.5), Days since stroke onset (Median)=5.0 (3.0–8.0),	**Intervention group:** oral fluoxetine 20 mg **Control group:** placebo **Frequency** in both groups: once daily for 6 months	mRS, SIS, Safety outcomes (fractures) at 6 months Followed-up at 12 months by postal questionnaire or telephone by one research nurse **Adverse events:** Hyponatraemia (<130 mmol/L) [EXP: 11 (1%); CON: 1 (<1%), p<0.01]

	Impairment/disability level: NIHSS Median (IQR)=3.0 (2.0–6.0)		
Dennis 2019 [47] PEDro score =10 (excellent) RCT	**EXP**: n=1564; Age: 71.2 (12.4); Days since stroke onset:6.9 (3.6) Impairment/disability level: NIHSS(Median)=6 (3–11) **CON**: n=1563; Age=71.5 (12.1): Days since stroke onset:7 (3.6) Impairment/disability level: NIHSS(Median)= 6 (3–11)	**Intervention group:** oral fluoxetine 20 mg **Control group:** placebo **Frequency** in both groups: once daily for 6 months	mRS, SIS, SF36, EQ5D-5L **Adverse events:** Falls with injury [EXP: 120 (7.7%); CON: 94 (6.0%), p=0.07]
Kraglund 2018 [46] PEDro score =9 (excellent) RCT	**EXP**: n=319; Age: mean(range; SD): 68 (24–97; 13).Years since stroke/TIA onset: within 7 days; Impairment/disability level: NIHSS: 5.3 (range, 0–27) **CON**: n=323; Age: mean(range; SD): 68 (19–99; 13);Years since stroke/TIA onset: within 7 days ; Impairment/disability level: NIHSS: 4.8 (range, 0–28)	**EXP**: citalopram **CON**: placebo **Frequency**: 20 mg daily (10 mg if aged ≥65 years or having reduced liver/kidney function) for 6 months	Fractures **Adverse events:** There was more non-cardiovascular death in EXP (n=10) than CON (n=3) (p=0.047), more urinary/genital symptoms in EXP (n=18) than CON (n=7) (p=0.02).
Viscoli 2017 [49] PEDro score =8 (excellent) RCT	**EXP**: n=1939; Age:63.5±10.6; Years since stroke/TIA onset: 6 months ; Disability level: MRS median (IQR): 1 (0–2) **CON**: n=1978; Age:63.5±10.7 ; Years since stroke/TIA onset: 6 months ; Disability level: MRS median (IQR): 1 (0–1)	**EXP:** pioglitazone **CON:** placebo **Frequency** in both groups: target dose, 45 mg daily for 4.8 years	Fractures **Adverse events:** More weight gain (>13.6Kg: 221 vs 88), edema (691 vs 483), shortness of breath (342 vs 292), happened in the pioglitazone group had than did participants in the placebo group.

Note: BMC: Bone mineral content; BMD: Bone mineral density; CMSA: Chedoke McMaster Stroke Assessment; CON: Control group; DXA: Dual-energy X-ray Absorptiometry; EQ5D-5L: EuroQol-5 Dimensions -5 Levels; EXP: Experimental group; FMA-UL/LL: Fugl-Meyer Assessment-upper limb/ lower limb; FIM: Functional Independence Measure; IQR: Interquartile Range; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; PT+OT: physical therapy + occupational therapy; RCT: randomized control trial; SIS: Stroke Impact Scale; SSS: Scandinavian Stroke Scale; TIA: transient ischemic attack; WBV: Whole body vibration.

Table 2: Methodological quality of reviewed non-pharmacological articles (PEDro)

	Shimizu 2002 [39]	Pang 2005 [8] & 2006 [9]	Pang, & Lau 2010 [36]	Tamura 2011 [38]	Pang 2013 [35]	Dennis 2013 [41]	Calugi 2016 [33]	Si 2016 [37]	Han 2017 [34]	Askim 2018 [40]	Yang 2021 [11]
Eligibility	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Subject random allocation	No	Yes	No	No	Yes	Yes	No	No	Yes	Yes	Yes
Allocation concealment	No	Yes	No	No	Yes	Yes	NR	No	No	Yes	Yes
Baseline similarities	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Subject Blinding	No	No	No	No	No	No	No	No	No	No	Yes
Therapist blinding	No	No	No	No	No	No	No	No	No	No	No
Assessor blinding	No	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes
>85% of outcomes obtained	Yes	Yes	Yes	No	Yes	No	Yes	No	No	No	Yes
Intention to treat	No	Yes	No	No	Yes	Yes	No	No	No	Yes	Yes
Between-group comparison	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Point measures of variability	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pedro score	**3**	**8**	**5**	**3**	**8**	**7**	**4**	**3**	**4**	**7**	**9**
Quality	poor	good	fair	poor	good	good	fair	poor	fair	good	excellent

Note: NR: not reported.

Table 3: Methodological quality of reviewed pharmacological/supplementation articles (PEDro)

	Treatments aimed at improving bone health					Investigation of adverse effects of pharmacological agents on Bone Health				
	Uebelhart 1999 [42]	Ikai 2001 [43]	Poole 2007 [25] & Poole 2009 [24]	Gommans 2013 [45]	Poulsen et al 2015 [44]	Viscoli 2017 [49]	Kraglund 2018 [46]	Dennis 2019 [47]	Hankey 2020 [27] & Hankey 2021 [26]	Lundström 2020 [48]
Eligibility	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Subject random allocation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Allocation concealment	NR	NR	Yes	NR	No	NR	Yes	Yes	Yes	Yes
Baseline similarities	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Subject Blinding	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Therapist blinding	Yes	NR	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Assessor blinding	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
>85% of outcomes obtained	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Intention to treat	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Between-group comparison	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Point measures of variability	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pedro score	**6**	**4**	**8**	**9**	**6**	**8**	**9**	**10**	**10**	**10**
Quality	good	fair	good	excellent	fair	good	excellent	excellent	excellent	excellent

Note: NR: not reported.

Table 4: Change score, Standardized effect size and confidence intervals of bone outcomes

Study	Site	Outcome	Experimental Group			Control Group			Hedge's	95% CI	
			Mean	SD	N	Mean	SD	N	G	Lower	Upper
Non-pharmacological intervention studies aimed at improving bone health											
Pang 2006 [9]	Tibia	P- area total (mm^2) 4% tibial-pQCT	21.20	23.00	18	-10.90	126.92	18	0.34	-0.31	1.00
	Tibia	P- Trab BMC (mg) 4% tibial-pQCT	11.00	54.67	18	0.50	47.01	18	0.20	-0.45	0.86
Multimodal lower limb exercise vs upper limb exercise	Tibia	P- Trab area (mm^2) 4% tibial-pQCT	37.20	21.00	18	-3.30	152.35	18	0.36	-0.29	1.02
	Tibia	P- Trab BMD (mg/cm^3) 4% tibial-pQCT	2.70	34.60	18	0.10	36.46	18	0.07	-0.58	0.73
	Tibia	NP- area total (mm^2) 4% tibial-pQCT	27.30	20.00	18	-11.50	129.99	18	0.41	-0.25	1.07
	Tibia	NP- Trab BMC (mg) 4% tibial-pQCT	10.30	47.70	18	-0.60	45.87	18	0.23	-0.43	0.88
	Tibia	NP- Trab Area (mm^2) 4% tibial-pQCT	33.70	18.00	18	-8.10	175.12	18	0.33	-0.33	0.99
	Tibia	NP- Trab BMD (mg/cm^3) 4% tibial-pQCT	2.50	30.61	18	0.60	41.32	18	0.05	-0.60	0.70
	Tibia	P-Total area (mm^2) 50% tibial-pQCT	-1.10	90.10	26	0.80	90.00	26	-0.02	-0.56	0.52
	Tibia	P- Area(cortical) (mm^2) 50% tibial-pQCT	1.70	74.71	26	-1.00	55.30	26	0.04	-0.50	0.58
	Tibia	P- Cort BMC (mg) 50% tibial-pQCT	1.30	87.01	26	-1.50	65.65	26	0.04	-0.51	0.58
	Tibia	P-Cortical BMD (mg/cm^3) -P 50% tibial-pQCT	-2.20	37.90	26	-1.40	30.89	26	-0.02	-0.57	0.52
	Tibia	P-Cortical thickness (mm) -P 50% tibial-pQCT	0.03	1.08	26	-0.04	0.95	26	0.07	-0.48	0.61
	Tibia	P- p-SSI (mm^3): women 50% tibial-pQCT	3.41	339.28	26	-0.20	197.03	26	0.01	-0.53	0.56
	Tibia	P- p-SSI (mm^3): men 50% tibial-pQCT	24.40	313.56	26	6.00	441.09	26	0.05	-0.50	0.59
	Tibia	NP- area total (mm^2) 50% tibial-pQCT	-5.20	86.85	26	-4.80	91.48	26	0.00	-0.55	0.54
	Tibia	NP- Area(cortical) (mm^2) 50% tibial-pQCT	-1.30	73.86	26	-0.30	56.30	26	-0.01	-0.56	0.53
	Tibia	NP- cortical BMC (mg) 50% tibial-pQCT	-0.60	86.85	26	-0.80	65.10	26	0.00	-0.54	0.55
	Tibia	NP- Cort BMD (mg/cm^3) 50% tibial-pQCT	1.10	47.64	26	-1.80	36.12	26	0.07	-0.48	0.61
	Tibia	NP- Cortical thickness (mm) 50% tibial-pQCT	-0.02	1.07	26	0.02	0.93	26	-0.04	-0.58	0.50
	Tibia	NP- p-SSI (mm^3): women 50% tibial-pQCT	-37.20	429.54	26	-14.90	236.45	26	-0.06	-0.61	0.48
	Tibia	NP- p-SSI (mm^3): men 50% tibial-pQCT	6.70	296.47	26	9.20	407.09	26	-0.01	-0.55	0.54
Pang 2005 [8] *Same as above*	Femoral neck	P-BMD (gm/cm^2) of femoral neck-DXA	-0.00	0.04	32	-0.02	0.03	31	**0.56***	**0.06**	**1.06**
	Femoral neck	NP-BMD (gm/cm^2) of femoral neck-DXA	0.01	0.03	32	0.00	0.03	31	0.36	-0.14	0.86
Pang 2010 [36] *progressive treadmill*	Tibia	P-cortical thickness (mm) of 66% tibia-pQCT	0.10	0.10	10	0.00	0.10	11	**0.96***	**0.06**	**1.86**
	Tibia	P-cortical BMD (mg/cm^3) of 66% tibia -pQCT	5.70	59.10	10	-7.50	76.10	11	0.18	-0.67	1.04

Study	Site	Outcome	Experimental Group			Control Group			Hedge's	95% CI	
			Mean	SD	N	Mean	SD	N	G	Lower	Upper
exercise vs usual care	Tibia	P-Total area (mm^2) of 66% site of tibia -pQCT	-1.90	14.30	10	-1.60	6.10	11	-0.03	-0.88	0.83
	Femur	P-BMD (g/cm^2) -total hip-P -DXA	0.00	0.01	10	-0.01	0.02	11	0.06	-0.79	0.92
Shimizu 2002 [39]	Upper limb	P-Upper extremity bone area-DXA (cm^2)	-2.00	40.06	5	10.80	24.90	5	-0.35	-1.60	0.90
Ball squeezing exercise + standard physical therapy (PT) vs standard PT alone	Upper limb	P-BMC (g) of upper limb-DXA	-4.60	34.87	5	2.80	29.54	5	-0.21	-1.45	1.04
	Upper limb	P-BMD (gm/cm^2) -UL-DXA	-0.02	0.10	5	0.00	0.12	5	-0.17	-1.41	1.07
	Upper limb	NP-Upper extremity bone area-DXA (cm^2)	-4.00	32.16	5	4.00	31.49	5	-0.23	-1.47	1.02
	Upper limb	NP-BMC (g) of upper limb-DXA	-5.80	33.02	5	-7.40	38.80	5	0.04	-1.20	1.28
	Upper limb	NP-BMD (gm/cm^2) -UL-DXA	-0.01	0.07	5	-0.02	0.17	5	0.09	-1.15	1.33
Yang 2021 [11] *Whole-body vibration training (WBV): 20Hz vs 30Hz*	serum	Cross-linked N-telopeptides of type I collagen (NTx)	-2.2	3.40	42	-2.7	4.00	42	0.13	-0.29	0.56
Pang 2013 [35] *Lower limb exercise with WBV vs same exercise without WBV*	serum	Cross-linked C-telopeptides of type I collagen (CTx)	0.27	0.27	41	0.25	0.25	41	0.08	-0.36	0.51
	serum	BALP-alkaline phosphatase (ng/ml)	-0.09	8.06	41	0.09	8.65	41	-0.02	-0.45	0.41
Han 2017 [34] *Daily upright bed weight training in female(F) and male (M): 30min vs 60min vs 90min*	Femoral neck	P-BMD (gm/cm^2) of M30 group-DXA[a]	0.00	0.11	25	0.07	0.12	25	-0.54	-1.11	0.02
	Femoral neck	P-BMD (gm/cm^2) of M60 group-DXA[b]	0.07	0.12	25	0.14	0.12	25	-0.58	-1.15	-0.02
	Femoral neck	P-BMD (gm/cm^2) of M90 group-DXA[c]	0.14	0.12	25	0.00	0.11	25	1.16	0.56	1.76
	Femoral neck	P-BMD (gm/cm^2) of of F30 group-DXA[a]	0.00	0.12	18	0.01	0.12	18	-0.07	-0.72	0.59
	Femoral neck	P-BMD (gm/cm^2) of of F60 group-DXA[b]	0.01	0.12	18	0.06	0.13	18	-0.41	-1.07	0.25
	Femoral neck	P-BMD (gm/cm^2) of of F90 group-DXA[c]	0.06	0.13	18	0.00	0.12	18	0.47	-0.19	1.13
	lumbar	BMD (gm/cm^2) of M30 group-DXA[a]	0.00	0.14	25	0.09	0.14	25	-0.62	-1.18	-0.05
	lumbar	BMD (gm/cm^2) of M60 group-DXA[b]	0.09	0.14	25	0.15	0.14	25	-0.48	-1.04	0.08
	lumbar	BMD (gm/cm^2) of M90 group-DXA[c]	0.15	0.14	25	0.00	0.14	25	**1.08***	**0.49**	**1.68**
	lumbar	BMD (gm/cm^2) of F30 group-DXA[a]	0.00	0.11	18	0.01	0.13	18	-0.04	-0.69	0.61
	lumbar	BMD (gm/cm^2) of F60 group-DXA[b]	0.01	0.13	18	0.08	0.12	18	-0.55	-1.21	0.12
	lumbar	BMD (gm/cm^2) of F90 group-DXA[c]	0.08	0.12	18	0.00	0.11	18	0.63	-0.04	1.30
Si 2016 [37]	Radius	P-BMD (g/cm^2) of Radius 33%-DXA	-0.05	0.12	26	-0.12	0.14	26	0.52	-0.03	1.08
	Femur neck	P-BMD (g/cm^2) of femoral neck-DXA	-0.09	0.12	26	-0.17	0.12	26	**0.63***	**0.07**	**1.18**

Study	Site	Outcome	Experimental Group			Control Group			Hedge's	95% CI	
			Mean	SD	N	Mean	SD	N	G	Lower	Upper
Conventional treatment (CT) + neuromuscular facilitation technique vs CT alone	Radius	NP-BMD (g/cm^2) of Radius 33%-DXA	0.01	0.11	26	-0.03	0.12	26	0.33	-0.22	0.87
	Femur neck	NP-BMD (g/cm^2) of femoral neck-DXA	-0.02	0.13	26	-0.04	0.15	26	0.14	-0.40	0.69
	Serum	Leptin	-1.84	2.64	26	-3.78	3.13	26	**0.66***	**0.10**	**1.22**
	Serum	ALP-alkaline phosphatase	34.31	20.79	26	18.14	21.62	26	**0.75***	**0.19**	**1.31**
	Serum	Osteocalcin	6.18	2.42	26	1.93	2.52	26	**1.69***	**1.06**	**2.33**
	Serum	IL-6-Interleukin-6	-19.39	30.44	26	43.61	33.88	26	**-1.93***	**-2.58**	**-1.27**
Tamura 2011 [38] *Daily hip bridges + standard rehabilitation vs standard rehabilitation alone*	Whole leg	P-leg bone mineral content (g)	-3.27	6.2	15	3.83	3.4	12	**-1.33**	**-2.17**	**-0.50**
		NP-leg bone mineral content (g)	4.93	3.9	15	-1.67	2.7	12	**1.87**	**0.96**	**2.78**
Dennis 2013 [41] *Intermittent pneumatic compression +usual care vs usual care alone*	NA	New bone fractures (No. events, Relative risk)	4		1438	4		1438	1.00	0.25	3.99
Calugi 2016 [33] *Adaptive physical activity + education vs education*	NA	New bone fractures (No. events, Relative risk)	2		93	8		89	0.24	0.05	1.10
Askim 2018 [40] *Progressed individualized coached exercise + standard care vs standard care*	NA	New bone fractures (No. events, Relative risk)	11		186	11		194	1.04	0.46	2.35
Pharmacological intervention studies aimed at improving bone health											
Uebelhart 1999 [42] *Salmon calcitonin +calcium +Bobath rehabilitation vs placebo +calcium +Bobath rehabilitation*	Serum	TAP-total alkaline phosphatase (U/litre)	2.00	26.51	11	-42.00	61.15	12	**0.89***	**0.03**	**1.74**
	Serum	OC-osteocalcin (ng/ml)	-3.10	6.79	11	1.80	9.55	12	-0.57	-1.40	0.27
	Serum	PICP-carboxy-terminal extension peptide of type I procollagen (µg/litre)	17.00	42.00	11	17.00	25.94	12	0.00	-0.82	0.82
	Serum	ICTP-cross-linked carboxy-terminal telopeptide of type I collagen (µg/litre)	-3.60	3.46	11	-6.50	9.64	12	0.38	-0.45	1.20
	Serum	Ca/cr-calcium/creatinine ratio	-0.29	0.38	11	-0.22	0.29	12	-0.20	-1.02	0.62
	Serum	OHP/cr-hydroxyproline/creatinine ratio	-7.40	14.80	11	-23.60	23.94	12	0.78	-0.07	1.62

Study	Site	Outcome	Experimental Group			Control Group			Hedge's	95% CI	
			Mean	SD	N	Mean	SD	N	G	Lower	Upper
	Serum	PIIINP-amino-terminal extension peptide of type III procollagen (U/ml)	-0.28	0.45	11	-0.26	0.54	12	-0.04	-0.86	0.78
Ikai 2001 [43]	lumbar	Low ADL-BMD -DXA (g/cm^2)	-0.40	3.70	18	-0.30	3.40	18	-0.03	-0.68	0.63
Etidronate + calcium+ rehabilitation exercise vs calcium+ rehabilitation exercise	Femur neck	Low ADL-BMD -P-DXA (g/cm^2)	-4.00	7.20	18	-9.60	5.90	18	**0.83***	0.15	1.51
	Femur neck	Low ADL-BMD -NP-DXA (g/cm^2)	-0.80	5.40	18	-3.70	5.20	18	0.53	-0.13	1.20
	lumbar	High ADL-BMD -DXA (g/cm^2)	-0.40	4.70	17	-0.10	3.90	19	-0.07	-0.72	0.59
	Femur neck	High ADL-BMD -P-DXA (g/cm^2)	-4.10	6.40	17	-4.60	6.50	19	0.08	-0.58	0.73
	Femur neck	High ADL-BMD-NP-DXA (g/cm^2)	-0.50	5.40	17	-2.60	4.40	19	0.42	-0.24	1.08
Poole 2007 [25]	Hip	Total hip BMD-P-DXA (g/cm^2)	0.00	0.02	14	-0.06	0.04	13	**1.53 #***	0.67	2.38
Zoledronate +supplementation vs placebo+ supplementation	Hip	Total hip BMD-NP-DXA (g/cm^2)	0.01	0.02	14	-0.03	0.03	13	**1.24 #***	0.42	2.06
Poole 2009 [24]	Hip	Total hip BMD-P-DXA (g/cm^2)	0.01	0.01	5	-0.03	0.04	9	**1.29#***	0.10	2.49
Zoledronate +supplementation vs placebo+ supplementation	Hip	Total hip BMD-NP-DXA (g/cm^2)	0.02	0.03	5	-0.01	0.03	9	0.76#	-0.37	1.89
Poulsen 2015 [44] *Modafinil vs placebo*	Whole body	BMD-DXA (g/cm^2)	0.02	0.04	7	0.02	0.02	11	0.24	-0.71	1.19
Gommans 2013 [45] *B-vitamins vs placebo*	NA	New bone fractures (No. events, Relative risk)	67		4089	78		4075	0.86	0.62	1.18
Investigations of adverse effects of other pharmacological interventions on bone health											
Hankey 2020 [27] *SSRI vs placebo*	NA	New bone fractures (No. events, Relative risk)	19		642	6		638	**3.15***	1.27	7.83
Lundström 2020 [48] *SSRI vs placebo*	NA	New bone fractures (No. events, Relative risk)	28		750	11		750	**2.55***	1.28	5.08
Dennis 2019 [47] *SSRI vs placebo*	NA	New bone fractures (No. events, Relative risk)	45		1564	23		1563	**1.96***	1.19	3.22
Kraglund 2018 [46] *SSRI vs placebo*	NA	New bone fractures (No. events, Relative risk)	7		319	1		323	7.09	0.88	57.28
Viscoli 2017 [49] *Pioglitazone vs placebo*	NA	New bone fractures (No. events, Relative risk)	218		1939	145		1937	1.53	1.24	1.89

Note: ADL: Activities of Daily Living; BMC: Bone mineral content; BMD: Bone mineral density; Cort: Cortical; DXA: Dual-energy X-ray Absorptiometry; P: paretic side; NP: non-

Study	Site	Outcome	Experimental Group			Control Group			Hedge's	95% CI	
			Mean	SD	N	Mean	SD	N	G	Lower	Upper

paretic side; pQCT: peripheral Quantitative Computed Tomography; Trab: Trabecular. SSRI: selective serotonin reuptake inhibitor (anti-depressant).
[a]: 30min VS 60min; [b]: 60min VS 90min; [c]: 30min VS 90min. [*]: Significant results. #: calculated based on percentage change in two groups; Hedge' G in bold: 95% CI not spanning zero.

Table 5: Quality of evidence: Grades of Recommendation, Assessment, Development, and Evaluation (GRADE)

Sub-group (Scanning machine used)	Outcome	Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	ES	Plausible residual confounding	Dose response gradient	Grade rating
Outcomes included in the meta-analysis: non-pharmacological interventions aimed at improving bone health											
Others (pQCT)	Total cross-sectional area (mm^2) of tibia	2	-1 a	0	0	-1 b c	0	0	0	0	Low
Cortical (pQCT)	Cortical thickness (mm) of tibia	2	-1 a	-1 e	0	-1 b c	0	0	0	0	Very Low
	Cortical BMD (mg/cm^3) of tibia	2	-1 a	0	0	-1 b c	0	0	0	0	Low
DXA	Total BMD (mg/cm^3) of hip	3	-1a	0	0	-1 b	0	0	0	0	Low
Serum bone biomarkers	Serum level of bone-specific alkaline phosphatase	2	0	-1 e	0	-1 b c	0	0	0	0	Low
	Serum resorption biomarkers	2	0	-1 e	0	-1 b c	0	0	0	0	Low
Outcomes included in the meta-analysis: side effect of pharmacological interventions											
Events	Fracture risk (anti-depressant)	4	0	0	-1g	0	0	+1	0	0	High
Outcomes not included in the meta-analysis: non-pharmacological interventions aimed at improving bone health											
Cortical (pQCT)	Cortical BMC of 50% Tibia (mg)	1	0	0	0	-2 d	0	0	0	0	Low
	Polar stress-strain index (mm^3) of 50% tibia	1	0	0	0	-2 d	0	0	0	0	Low

Sub-group (Scanning machine used)	Outcome	Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	ES	Plausible residual confounding	Dose response gradient	Grade rating
Trabecular (pQCT)	trabecular BMC (mg) of 4% tibia	1	0	0	0	-2 d	0	0	0	0	Low
	trabecular area (mm^2) 4% tibia	1	0	0	0	-2 d	0	0	0	0	Low
	trabecular BMD (mg/cm^3) 4% tibia	1	0	0	0	-2 d	0	0	0	0	Low
Other bone measures (DXA)	Upper Extremity BMD (gm/cm^2)	2	-2 a	0	0	-1 b c	0	0	0	0	Very low
	Upper extremity bone area (cm^2)	1	-1 a	0	0	-2 d	0	0	0	0	Very Low
	Upper extremity BMC (g)	1	-1 a	0	0	-2 d	0	0	0	0	Very Low
	femoral neck BMD (gm/cm^2)	2	0	0	0	-2 d	0	0	0	0	Low
	BMD (gm/cm^2) of lumbar vertebra	1	-1 a	0	0	-2 d	0	0	0	0	Very Low
Serum bone markers (/)	Cross-linked N-telopeptides of type I collagen	1	0	0	0	-2 d	0	0	0	0	Low
	C-telopeptide of type I collagen cross-links (CTx)	1	0	0	0	-2 d	0	0	0	0	Low
Events	Fracture risk (intermittent pneumatic compression)	1	0	0	-1 g	-2 d	0	0	0	0	Very Low
Events	Fracture risk (exercise)	2	-1 a	0	-1 g	-1d	0	0	0	0	Low
Outcomes not included in the meta-analysis: pharmacological/supplementation interventions aimed at improving bone health											

Sub-group (Scanning machine used)	Outcome	Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	ES	Plausible residual confounding	Dose response gradient	Grade rating
Total (DXA)	Total BMD (mg/cm^2) of hip (anti-absorptive agents)	2	0	0	-1 g	-1 d	0	0	0	0	Low
Total (DXA)	Total BMD (mg/cm^2)-unspecific site (modafinil)	1	0	0	0	-2 d	0	0	0	0	Low
Outcomes not included in the meta-analysis: adverse effect of other pharmacological/supplementation interventions on bone health											
Events	Fracture risk (pioglitazone)	1	0	0	-1 g	-2 d	0	0	0	0	Very low
Events	Fracture risk (B-vitamins)	1	0	0	-1 g	-2 d	0	0	0	0	Very low

Note: ES: effect size; BMC: Bone mineral content; BMD: Bone mineral density; pQCT: peripheral Quantitative Computed Tomography; DXA: Dual-energy X-ray Absorptiometry.(a) For outcomes if less than half of the participants were from trials with PEDro scores larger or equal to 6; (b) Insufficient studies for meta-analysis and the number of subjects included in the meta-analysis was below 400; (c)The 95% CI spanned 0; (d) Insufficient studies for meta-analysis (Imprecision); (e) For outcomes included in the meta-analysis, I^2 value is larger or equal to 50% in the meta-analysis; (g) The participants, intervention, comparator intervention, outcome measure, or study design did not match between the included studies and the eligibility criteria for this review.