Exercise Reduces the Number of Overall and Major Osteoporotic Fractures in Adults. Does Supervision Make a Difference? Systematic Review and Meta-Analysis

Isabelle Hoffmann,1 Mahdieh Shojaa,2,3 Matthias Kohl,3† Simon von Stengel,1† Clemens Becker,4† Markus Gosch,5† Franz Jakob,5† Katharina Kerschan-Schinfl,6† Bernd Kladny,6 Jürgen Clausen,9† Uwe Lange,8† Stefan Middeldorf,11† Stefan Peters,12† Daniel Schoene,13† Cornél Sieber,13† Reina Tholen,14† Friederike Thomasius,15† Heike A Bischoff-Ferrari,16† Michael Uder,17 and Wolfgang Kemmler1,17†

1Institute of Medical Physics, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany
2Institute of Health Science, Department of Population-Based Medicine, University Hospital Tübingen, Tübingen, Germany
3Department of Medical and Life Sciences, University of Furtwangen, Schwenningen, Germany
4Robert-Bosch-Hospital, Geriatrics and Geriatric Rehabilitation, Stuttgart, Germany
5Paracelsus Medical University Nürnberg and General Hospital Nürnberg, Nuremberg, Germany
6Bernhard Heine Centre of Movement Science, University of Würzburg, Würzburg, Germany
7Austrian Society for Bone and Mineral Research, Vienna, Austria
8German Society for Orthopaedics and Trauma, Frankfurt, Germany
9Deutscher Rheuma-Liga Bundesverband e.V, Bonn, Germany
10German Society for Physical and Rehabilitative Medicine, Ulm, Germany
11International Musculoskeletal Pain Society, Ravensburg, Germany
12German Association for Health-Related Fitness and Exercise Therapy (DVGS) e.V, Hürth-Efferen, Germany
13European Geriatric Medicine Society (EuGMS), Institute for Biomedicine of Aging, FAU Erlangen-Nürnberg, Nürnberg, Germany
14Deutscher Verband für Physiotherapie (ZVK) e.V, Köln, Germany
15Osteology Umbrella Association Germany, Austria, Switzerland
16Department of Geriatrics and Aging Research, University Hospital of Zurich, City Hospital of Zurich-Waid and University of Zurich, Centre on Aging and Mobility, University of Zurich, Zürich, Switzerland
17Institute of Radiology, University Hospital Erlangen, Erlangen, Germany

ABSTRACT

The purpose of this systematic review and meta-analysis (PROSPERO ID: CRD42021250467) was to evaluate the effects of exercise on low-trauma overall and major osteoporotic fractures (hip, spine, forearm, or humerus fractures) and to determine the corresponding effect of supervision of the exercise program. Our systematic search of six literature databases according to the PRISMA guideline was conducted from January 1, 2013 (ie, date of our last search) to May 22, 2021, and included controlled clinical exercise trials with (i) individuals aged ≥45 years, (ii) cohorts without therapies/diseases related to fractures, (iii) observation periods of ≥3 months, and (iv) the number of low-trauma fractures listed separately for the exercise (EG) and control (CG) groups. We included 20 intervention studies with 21 EGs and 20 CGs comprising a pooled number of participant-years of n = 11.836 in the EG and n = 11.275 in the CG. The mixed-effects conditional Poisson regression revealed significant effects of exercise on low-trauma overall incidence (rate) ratio (IR 0.67, 95% confidence interval [95% CI] 0.51–0.87) and major osteoporotic fractures IR (0.69, 95% CI 0.52–0.92). Heterogeneity between the trials was moderate for low-trauma overall (I2 = 40%) and negligible (I2 < 1%) for major osteoporotic fractures. Supervision of the exercise program plays a significant role in the reductions of overall and major osteoporotic fractures with IR about twice as favorable in the predominantly supervised (IR 0.44; 95% CI 0.27–0.73 and 0.38; 0.19–0.76) versus the predominately non-supervised exercise trials (IR 0.83; 95% CI 0.60–1.14 and 0.82; 0.64–1.05). In summary, the present study provides evidence for the positive effect of exercise on low-trauma overall and major osteoporotic fractures in middle aged to older adults. Supervision of the exercise program...
program is a crucial aspect in exercise programs on fracture reduction. Thus, home-based exercise protocols should increasingly implement online classes to ensure widely consistent supervision and monitoring of the exercise program. © 2022 The Authors. Journal of Bone and Mineral Research published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: EXERCISE; LOW-TRAUMA FRACTURE; OVERALL FRACTURES; OSTEOPOROTIC FRACTURES

Introduction

Low-trauma fractures related to osteoporosis are a major problem in our aging society. Apart from the far-reaching individual consequences, the 4.3 million fragility fractures incur costs for the European health care systems of EUR 56 billion a year. (1) Given the demographic change in Europe, the number of osteoporotic fractures will likely increase by 25% during the next 10 to 15 years. (1) Because of its favorable effects on fall risk (2) and bone strength, (3,4) physical exercise seems to be a promising strategy for preventing fractures in adults. Indeed, the few meta-analyses on this issue provide positive evidence for the fracture-preventing effect of exercise in older adults. (5,6) In detail, however, effect sizes vary considerably between the analyses. This can be partially attributable to the types of fractures addressed. While three meta-analyses focus on fall-related fractures, (5,7,8) only one study focuses on low-trauma overall fractures in middle-aged to older adults. (9) The latter study (6) does demonstrate a significant, large-sized effect of exercise on overall fracture incidence (incidence rate ratio [IR] 0.49; 95% confidence interval [95% CI] 0.31–0.76). However, that strong evidence of positive effects of exercise on fracture reduction (9) might be considerably weakened in particular by two recent studies (5,10) that applied predominately non-supervised exercise protocols. Although this approach allows for cost-effective conducting of large clinical trials, it possibly comes at the price of quality (11,12) and effectiveness (13,14) of the exercise intervention. Moreover, no exercise trial to date has been dedicated to fractures closely related to osteoporosis (i.e., major osteoporotic fractures) (15). In summary, an update on the effect of exercise on fracture incidence appears called for. (15) The purpose of this systematic review and meta-analysis is thus to provide evidence for a positive effect of exercise on fracture incidence and to identify corresponding differences due to supervision. Our primary hypothesis was that exercise significantly reduces the number of low-trauma overall fractures and major osteoporotic fractures following FRAX (13) compared with a control group. We further hypothesize that the effect of predominately supervised exercise programs is superior to predominately non-supervised exercise programs.

Materials and Methods

This meta-analysis used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (17). The study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under ID: CRD42021250467.

Eligibility criteria

Inclusion criteria

Included were clinical trials of exercise that focus on fracture prevention with human adults. In detail, we included articles that meet the following criteria: (i) randomized or non-randomized clinical trials with at least one exercise (EG) versus one control group (CG); (ii) participants (female, male, or mixed cohorts) were aged 45 years and older; (iii) studies that focus on fracture prevention, fall reduction, improvement of bone strength; (iv) the number of fractures was reported separately for EG and CG as endpoint, secondary endpoint, observation, or adverse event; (v) outcome measures were all kinds of fractures, including overall fractures, major osteoporotic fractures, and local fractures independent of the skeletal location; (vi) the study was carried out for at least 3 months.

Exclusion criteria

We excluded studies with participants (i) undergoing pharmacological therapy with relevant positive (e.g., hormone replacement therapy) or negative (glucocorticoids) effect on bone metabolism, (ii) undergoing chemo- and/or radiotherapy, or (iii) trials/study groups with mixed interventions (i.e., exercise and high-dosed vitamin D or omega 3 fatty acids (10)). Preliminary data, duplicate studies, review articles, case reports, editorials, conference abstracts, and letters were not considered either.

Information sources

An overall search was performed in six electronic databases (PubMed, Scopus, Web of Science, Cochrane, Science Direct, and ERIC) for all articles published from January 1, 2013 (i.e., date of our last search (6)) to May 1, 2021, with no language restrictions.

Literature search

A standard protocol for this search was developed and a controlled vocabulary (Mesh term for medline) was used. Keywords and their synonyms were used by applying the following queries “Bone mass” or “Osteopenia” or “Bone turnover” or “Bone metabolism” or “Bone mineral content” or “Skeleton” or “Bone mineral density” or “BMD” or “Bone density” or “Osteoporoses” or “Osteoporosis” or “Bone structure” or “Bone tissue” or “Bone” AND (“Bone fracture” or “Fracture” or “Fragility fracture” or “Broken bone”) AND (“Exercise” or “Physical activity” or “Physical training” or “Exercise training”) AND (“Clinical trial”) AND (“<45 years old”).

To identify more relevant studies, reference lists of included articles or reviews dealing with the effect of exercise on BMD or fall reduction were screened. Articles were excluded, when no full text was available or the reports were unpublished. If relevant eligibility data were missing, the authors were contacted by e-mail (n = 4).

Considering that many studies focus on fall-related fractures (9-20,21,30,33,37,38,40-42,44) and/or exclude vertebral fractures (45), the number of vertebral fractures will be considerably underestimated.
Data extraction

IH and MS separately and independently reviewed titles and abstracts for eligible articles. Then the full-text articles were checked by IH and WK. Study data were extracted by IH and WK with any disagreement being resolved by discussion. Data from included articles were checked using a detailed extraction form that determined: (i) publication details (eg, first author’s name, publication year); (ii) study characteristics (eg, design, length of the study, initial sample size); (iii) study protocol (eg, intervention, focus of the intervention); (iv) participant characteristics (eg, sex, age); (v) exercise characteristics including intervention length, type of exercise, exercise parameters (eg, exercise frequency, intensity, duration, cycle number), intensity progression, adherence, number of withdrawals, supervision of the session, etc.; (vi) supplementation with nutritional supplements; and (vii) fractures as described below in the EG and CG (Tables 1 and 2).

Outcome measures

Outcomes of interest were overall fractures and major osteoporotic fractures defined as a fracture of the hip, spine, forearm, or humerus according to FRAX.\(^\text{[13]}\) We aimed to focus exclusively on low-trauma fractures; ie, fractures induced by car or bicycle accidents, falls from levels higher than standing, or other high trauma were excluded. Deviating from FRAX,\(^\text{[15]}\) all types of humerus fractures were considered. In parallel, morphometric fractures (ie, vertebral deformity/reduction of vertebral body height) as assessed by radiographs of the spine were also considered as vertebral fractures.

Quality assessment

To evaluate the methodologic quality of the trial, the articles were assessed separately and independently by two reviewers (IH, WK) utilizing the PEDro (physiotherapy evidence database scale risk of bias tool)\(^\text{[36]}\) and the TESTEX (tool for the assessment of study quality and reporting in exercise) score.\(^\text{[37]}\) In particular, the latter tool is specifically dedicated to exercise studies. Of importance, the scores were awarded on the basis of the exercise intervention of the trials. In cases of inconsistency, a third reviewer decided (SvS).

Data synthesis

For the trial of Karinkanta and colleagues\(^\text{[24]}\), we pooled their three exercise groups with different types of exercise (Table 2). The subgroup analyses focused on differences in the degree of supervision of the exercise session. Based on the number of sessions per week prescribed by the articles and considering the corresponding attendance rate(s), IH and WK classified the exercise protocols into “predominately supervised” (PS) and “predominately non-supervised” (PNS) interventions. To adequately address the issue of supervision, we excluded the three follow-up (FU) studies\(^\text{[34,35,38]}\) that determined the effect on fractures 5 or 8 years after the end of the exercise intervention.

Statistical procedures

We followed the recommendations of Stijnen and colleagues\(^\text{[39]}\) and used a mixed-effects conditional Poisson regression model for our analysis. In addition, we adopted Efthimiou\(^\text{[40]}\) and compared the results of this analysis with the results using the approach of Mantel–Haenszel.\(^\text{[41]}\) We applied R packages metafor\(^\text{[42]}\) and mmeta\(^\text{[43]}\) included in the statistical software R.\(^\text{[44]}\)

The incidences were transformed into incidence rate ratios along with 95% confidence intervals. For the study of Iliffe and colleagues\(^\text{[23]}\) with two exercise groups, the control group was split into two smaller groups for comparison against each intervention group.\(^\text{[45]}\) Funnel plots with Kendall’s \(\tau\) statistic were applied to explore potential small study/publication bias. Subgroup analyses were applied for subgroups as described in data synthesis above.

Assessment of heterogeneity and small study effects

The \(I^2\) statistic\(^\text{[45]}\) in combination with a Wald and likelihood-ratio test were applied to identify the fraction of variance that is due to heterogeneity among the studies included in the given analysis. Funnel plot visually determined the relation between effect size and sample size to identify small study/publication bias. Rank correlation tests were applied to determine funnel plot asymmetry.\(^\text{[46]}\)

Results

Our search identified 20 studies\(^\text{[9,10,18-32,34,35,38]}\) with 21 exercise groups and 20 control groups (Fig. 1) that reported eligible fractures. The pooled number of participant-years was \(n = 23,111\) (EG: \(n = 11,836\), CG: \(n = 11,275\)). Correspondingly, data of 14 studies\(^\text{[9,10,19,20,22,24-27,30,31,34,35,38]}\) with a pooled number of participant-years of \(n = 10,920\) in the EG and \(n = 10,312\) in CG were included in the analysis on major osteoporotic fractures. Although not always fully described, at least 12 studies\(^\text{[9,10,18,22-25,27-29,31,38]}\) recorded exclusively fall-related or non-vertebral fractures. Three of the 20 trials were “FU studies” conducted \(5\)\(^\text{[34,38]}\) or 8 years\(^\text{[45]}\) after the end of the exercise intervention (Tables 1 and 2).

Study and participant characteristics of the studies

Table 1 gives a summary of the study and participant characteristics. All the studies included community-dwelling, middle-aged to older people. Apart from two studies\(^\text{[19,32]}\), all the studies included White cohorts between 45 and 95 years old. Initial sample sizes varied from \(27\) to \(3279\) participants/group, while participant years varied between \(67\)\(^\text{[18,19]}\) and \(4919\) years\(^\text{[9]}\) in the EGs, and \(67\)\(^\text{[19]}\) to \(4835\) years\(^\text{[9]}\) in the CGs. Eleven studies exclusively considered women. The trials were conducted in Australia\(^\text{[21]}\), Austria\(^\text{[30]}\), Canada\(^\text{[28]}\), China\(^\text{[19]}\), Finland\(^\text{[24,27,34,38]}\), Germany\(^\text{[25,26]}\), Japan\(^\text{[2]}\), New Zealand\(^\text{[31]}\), the UK\(^\text{[9,18,20,23,29]}\), the US\(^\text{[22,35]}\) and another study was a multicenter study in five European countries\(^\text{[10]}\). Six studies defined fractures risk as the primary outcome (Table 1).

Exercise characteristics

Table 2 displays exercise characteristics of the included studies. Multicomponent exercise protocols were applied by 10 studies (Table 2). Resistance exercise was a component in 14 study arms (Table 2). Length of intervention ranged from 6 weeks\(^\text{[18]}\) to 16 years\(^\text{[26]}\); net exercise frequency of most studies averaged \(\geq 2\) sessions/week. Unfortunately, not all studies adequately and comprehensively reported the exercise intensity applied for the respective training components (Table 2). In parallel, progression of intensity was realized in 11 studies; however, this aspect might be irrelevant in interventions \(\leq 6\) months. In 13 study arms,
Table 1. Study and Participant Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>First author, year, study-type, reference</th>
<th>Stud length (months)</th>
<th>Age (years), status</th>
<th>Female sex</th>
<th>Body mass index, (kg/m²)</th>
<th>Initial sample size (n)</th>
<th>Dropout (%)</th>
<th>Specific characteristics of the study group</th>
<th>Medication (%)</th>
<th>Fracture as the primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashburn et al., 2007, RCT[18]</td>
<td>6</td>
<td>45–91 cdw</td>
<td>EG: 46%</td>
<td>n.g. EG: 70</td>
<td>12</td>
<td>Yes</td>
<td>People with Parkinson’s disease, more than one fall last 12 months</td>
<td>EG: ≥89</td>
<td>No</td>
</tr>
<tr>
<td>Bischoff-Ferrari et al., 2020, RCT[20]</td>
<td>36</td>
<td>75 ± 4 cdw</td>
<td>EG: 62%</td>
<td>26.3 ± 4.2 EG: 267</td>
<td>Total: 12</td>
<td>Yes</td>
<td>No major health events, sufficiently mobile, good cognitive status, ≥40% with fall history</td>
<td>EG: ≥48</td>
<td>Yes</td>
</tr>
<tr>
<td>Chan et al., 2004, RCT[19]</td>
<td>12</td>
<td>54 ± 4 cdw</td>
<td>EG: 100%</td>
<td>24.1 ± 4.7 EG: 67</td>
<td>19</td>
<td>Yes</td>
<td>Early-postmenopausal healthy women without a history of fractures</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Ebrahim et al., 1997, RCT[20]</td>
<td>24</td>
<td>67 ± 8 n.g.</td>
<td>EG: 100%</td>
<td>23.5 ± 4.6 EG: 81</td>
<td>Total: 41</td>
<td>No</td>
<td>Women with upper limb fractures during the last 2 years</td>
<td>EG: ≥7</td>
<td>No</td>
</tr>
<tr>
<td>Gianouidis et al., 2014, RCT[21]</td>
<td>12</td>
<td>67 ± 6 cdw</td>
<td>EG: 74%</td>
<td>27.2 ± 3.8 EG: 81</td>
<td>6</td>
<td>No</td>
<td>No osteoporosis or low-trauma fracture in the past 6 months</td>
<td>EG: 5.3</td>
<td>Yes</td>
</tr>
<tr>
<td>Gill et al., 2016, RCT[22]</td>
<td>31</td>
<td>79 ± 5 n.g.</td>
<td>EG: 67%</td>
<td>30.1 ± 5.7 EG: 818</td>
<td>n.g.</td>
<td>Yes</td>
<td>Functional limitations (SPPB ≤9; but 400 m ≤15 min) Walking independently indoors and outdoors (with/without a walking aid but without help)</td>
<td>CG: 5.4</td>
<td>Yes</td>
</tr>
<tr>
<td>Iliffe et al., 2014, cluster-RCT[23]</td>
<td>6</td>
<td>65–94 cdw</td>
<td>FaME: 62%</td>
<td>26.9 ± 5.0 FaME: 38</td>
<td>All: 4</td>
<td>No</td>
<td>No diseases or medication relevantly affecting falls or bone strength, no osteoporosis</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Karinkanta et al., 2007, RCT[24]</td>
<td>12</td>
<td>70–79 cdw</td>
<td>EG: 100%</td>
<td>28.1 ± 3.8 EG: 112</td>
<td>4</td>
<td>Yes</td>
<td>No osteoporosis</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Kemmler et al., 2010, RCT[25]</td>
<td>18</td>
<td>69 ± 4 cdw</td>
<td>EG: 100%</td>
<td>26.1 ± 4.0 EG: 123</td>
<td>7</td>
<td>No</td>
<td>No diseases or medication relevantly affecting falls or bone strength</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Kemmler et al., 2015, CT[26]</td>
<td>16 yrs</td>
<td>55 ± 3 cdw</td>
<td>EG: 100%</td>
<td>25.7 ± 3.4 EG: 86</td>
<td>31</td>
<td>Yes</td>
<td>Early-postmenopausal (1–8 years) women with osteopenia; no diseases/medication relevantly affecting falls or bone strength</td>
<td>None</td>
<td>Yes</td>
</tr>
</tbody>
</table>

(Continues)
predominantly non-supervised exercise training was applied, whereas six studies scheduled a predominantly supervised joint/group-exercise program (Table 2). With respect to physical interventions in the control group, at least three studies implemented a physically active control.

Supplementation with vitamin D and/or calcium

Three studies provided vitamin D (500–1000 IU/d) and calcium (700–1000 mg/d) supplements for the EG and CG. In the study of McMurdo and colleagues, 1000 mg/d calcium for both study arms was supplied.

Methodological quality

The methodological quality using PEDro and the TESTEX scale is listed in Table 3. Score points vary between 3 and 9 of a maximum of 10 (9) points for PEDro and 6 to 14 of a maximum of 15 for the TESTEX score. Of importance, blinding of instructors (ie, caregivers) is not realistic in exercise studies; consequently, the maximum score that can be awarded for PEDro is 9 points. Of importance, blinding of instructors (ie, caregivers) is not realistic in exercise studies; consequently, the maximum score that can be awarded for PEDro is 9 points. In contrast to PEDro, TESTEX did not score blinding of caregivers and participants.

Altogether, we observed 368 fractures in the EG and 423 fractures in the CG. In parallel, we observed 151 major osteoporotic fractures in the EG and 196 in the CG. Although not all studies

### Table 1. Continued

<table>
<thead>
<tr>
<th>First author, year, study-type, reference</th>
<th>Stud length (months)</th>
<th>Age (years), status</th>
<th>Female sex</th>
<th>Body mass index (kg/m²)</th>
<th>Initial sample size (n)</th>
<th>Dropout (%)</th>
<th>Specific characteristics of the study group</th>
<th>Medication (%)</th>
<th>Fracture as the primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korpelainen et al., 2006, RCT</td>
<td>30</td>
<td>70–73 cdw</td>
<td>EG: 100%</td>
<td>25.7 ± 3.4</td>
<td>EG: 84</td>
<td>EG: 18</td>
<td>Low BMD at the proximal femur or distal radius (&lt; −2 SD T-score)</td>
<td></td>
<td>n.g. No</td>
</tr>
<tr>
<td>Lamb et al., 2020, cluster-RCT</td>
<td>18</td>
<td>78 ± 6 cdw</td>
<td>EG: 53%</td>
<td>27 ± 5</td>
<td>EG: 2729</td>
<td>EG: 16</td>
<td>People at increased risk for falls (risk screening questionnaire)</td>
<td></td>
<td>n.g. Yes</td>
</tr>
<tr>
<td>Liu et al., 2019, RCT</td>
<td>12</td>
<td>81 ± 6 cdw</td>
<td>EG: 64%</td>
<td>26.9 ± 5.4</td>
<td>EG: 173</td>
<td>Total: 14</td>
<td>History of fall last 12 months; recruited from a fall prevention clinic</td>
<td></td>
<td>n.g. No</td>
</tr>
<tr>
<td>McMurdo et al., 1997, RCT</td>
<td>24</td>
<td>60–73 cdw</td>
<td>EG: 100%</td>
<td>n.g.</td>
<td>EG: 58</td>
<td>EG: 24</td>
<td>No conditions or medication relevantly affecting bone strength</td>
<td></td>
<td>n.g. No</td>
</tr>
<tr>
<td>Preisinger et al., 1996, RCT</td>
<td>48</td>
<td>45–75 cdw</td>
<td>EG: 100%</td>
<td>n.g.</td>
<td>EG: 27</td>
<td>EG: 56</td>
<td>Moderate back complaints, no medication relevantly affecting bone strength</td>
<td></td>
<td>n.g. No</td>
</tr>
<tr>
<td>Robertson et al., 2001, RCT</td>
<td>12</td>
<td>75–95 cdw</td>
<td>EG: 68%</td>
<td>n.g.</td>
<td>EG: 121</td>
<td>10</td>
<td>Ability to walk around own residence</td>
<td></td>
<td>EG: 3.0 No</td>
</tr>
<tr>
<td>Sakamoto et al., 2012, RCT</td>
<td>6</td>
<td>ca. 81 ± 4 cdw</td>
<td>EG: 79%</td>
<td>23.2 ± 23.2</td>
<td>EG: 714</td>
<td>EG: 43</td>
<td>People with leg standing time ≤15 seconds; no other conditions relevantly affecting fall risk</td>
<td></td>
<td>n.g. Yes</td>
</tr>
</tbody>
</table>

Cdw = community dwelling; CT = controlled trial; FaME = fall management exercise; FU = follow-up; n.g. = not given; OEP = Otago Exercise Program; RCT = randomized controlled trial. Shaded rows = studies on major osteoporotic fractures.

*Only medication with a moderate impact on falls or bone strength.

Overall number of drugs.

Serious fall injury: “fall resulting in a clinical non-vertebral fracture or that led to hospital admission.”

We included the “fully compliant subgroup.”

Based on body height and mass reported by the authors.
<table>
<thead>
<tr>
<th>First author, year, reference</th>
<th>Focus of the intervention</th>
<th>Design, supervision length of intervention</th>
<th>Type of exercise in the EG; (supplementation with Ca and vitamin D)</th>
<th>Exercise/strain composition</th>
<th>Progression of intensity</th>
<th>Attendance rate</th>
<th>Type of exercise/intervention in the CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashburn et al., 2007(18)</td>
<td>Fall prevention</td>
<td>IE-PNS 6 weeks</td>
<td>Multi component: walking, lower-extremity DRT, flexibility, balances; no dietary supplements (vitamin D, Ca, protein) DRT; no supplements</td>
<td>Individualized exercise with 6 levels of progression. First 6 weeks: led by a physiotherapist (once per week?), no further details given</td>
<td>Yes</td>
<td>n.g.</td>
<td>No physical intervention (contact with nurse)</td>
</tr>
<tr>
<td>Bischoff-Ferrari et al., 2020(10)</td>
<td>n.g.</td>
<td>IE-PNS 36 months</td>
<td>3 × 30 minutes/week, 5 resistance exercises (sit to stand, one-leg stance, pull backs, external shoulder rotation steps), participants received an instruction by a physiotherapist at baseline and every 3 months and video and paper manuals given</td>
<td>No</td>
<td>70%b ≥2 seconds/week 62% ≥ 3 seconds/week</td>
<td>Flexibility, 5 exercises for hip, knee, trunk chest, shoulder, and ankle mobility, 3 × 30 minutes/week</td>
<td></td>
</tr>
<tr>
<td>Chan et al., 2004(19)</td>
<td>Bone strength</td>
<td>JE-PS 12 months</td>
<td>Tai Chi Chun, Yang style; no supplements</td>
<td>5 × 50 minutes/week; all main muscle groups, no details given</td>
<td>No</td>
<td>84%</td>
<td>No intervention</td>
</tr>
<tr>
<td>Ebrahim et al., 1997(20)</td>
<td>Bone strength and fall reduction</td>
<td>IE-PNS 24 months</td>
<td>Brisk walking; no supplements</td>
<td>3 × 40 minutes/week brisk walking presumably with moderate intensity (details n.g.)</td>
<td>No</td>
<td>100%</td>
<td>Exercises for the upper limb; (details n.g.) study nurse-visits</td>
</tr>
<tr>
<td>Gianoudis et al., 2014(21)</td>
<td>Bone strength and fall prevention</td>
<td>IE-PS 12 months</td>
<td>Multi component: high-velocity DRT at machines and free weights, WB-/impact exercise, balance; 1000 IU/d vitamin D, 700 mg/d Ca</td>
<td>3 × 60 minutes/week; DRT: 6 exercises, 2 sets × 8–12 reps at 5–8 RPE (Borg CR10) explosive movements during concentric phase; WB: 2 exercises, 3 sets × 10–20 stamps/hops/jumps; 2 balance exercises à 30–60 seconds</td>
<td>Yes</td>
<td>74%</td>
<td>No physical intervention, information about osteoporosis</td>
</tr>
<tr>
<td>Gill et al., 2016, RCT(22)</td>
<td>Fall prevention</td>
<td>IE-PNS 26 months</td>
<td>Multi component: walking, lower-extremity DRT, flexibility exercises for major muscle groups, balance; no supplements</td>
<td>In total: 5–6 × 30 minutes/ week; presumably 2–3x 30 minutes/week walking at RPE 13 (Borg CR-20), 3 × week 5 DRT exercises 2 sets × 10 reps at RPE 15–16 (CR 20), 10 minutes of balance exercise and 3–5 minutes of stretching</td>
<td>Yes</td>
<td>63%</td>
<td>No physical intervention, health education program</td>
</tr>
<tr>
<td>First author, year, reference</td>
<td>Focus of the intervention</td>
<td>Design, supervision length of intervention</td>
<td>Type of exercise in the EG: (supplementation with Ca and vitamin D)</td>
<td>Exercise/strain composition</td>
<td>Progression of intensity</td>
<td>Attendance rate</td>
<td>Type of exercise/intervention in the CG</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------------------------</td>
<td>------------------------------------------</td>
<td>-------------------------------------------------------------</td>
<td>-----------------------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Iliffe et al., 2014, cluster-RCT&lt;sup&gt;(23)&lt;/sup&gt;</td>
<td>Bone strength and fall prevention</td>
<td>FaME: JE/IE-PNS 6 months</td>
<td>Multi-component: endurance including walking, DRT with free weights, floor exercises, axial loading, balance, flexibility; no supplements</td>
<td>In total 5 sessions/week; 1 × 60 minutes/week DRT, floor exercises, cardiovascular exercises, “challenging” balance exercises; 2 × 30 minutes/week home exercise based on OEP (however more “intense”); 2 × 30 minutes walking at moderate pace; details n.g.</td>
<td>Yes</td>
<td>n.g. (&lt;40%)</td>
<td>No intervention</td>
</tr>
<tr>
<td>Fall prevention</td>
<td>OEP: IE-PNS&lt;sup&gt;6&lt;/sup&gt; 6 months</td>
<td>Multi-component: walking, DRT with free weights, balance; no supplements</td>
<td></td>
<td>In total ≥3 × 30 minutes/week; 5 DRT-exercises with 4 intensity levels up to 2 sets of 10 reps; and 12 balance exercises with 4 intensity levels; up to 4 sets of 10 steps; 2 × 30 minutes walking with habitual speed</td>
<td>Yes</td>
<td>n.g. (&lt;40%)</td>
<td></td>
</tr>
<tr>
<td>Karinkanta et al., 2007&lt;sup&gt;(24)&lt;/sup&gt;</td>
<td>Bone strength</td>
<td>JE-PS, 12 months</td>
<td>DRT for all main muscle groups versus balance and high impact exercise versus multi-component: (DRT, impact, balance); no supplements</td>
<td>3 × 45–50 minutes/week; DRT: 7 exercises, 3 sets, reps 8–10 reps at 75–80% 1RM</td>
<td>Yes</td>
<td>67%</td>
<td>No intervention</td>
</tr>
<tr>
<td>Kemmler et al., 2010&lt;sup&gt;(25)&lt;/sup&gt;</td>
<td>Bone strength and fall prevention</td>
<td>JE/IE-PS, 18 months</td>
<td>Multi-component: aerobic dance, DRT, functional gymnastics, isometric exercise; 500 IU vitamin D/d; 1000 mg/d Ca.</td>
<td>In total 4 sessions/week; 2 × 60 minutes/week JE-S, aerobic dance at 70–85% HRmax; static/dynamic balance exercises, isometric/ floor exercises at RM, 3 upper body exercises with 2–3 sets, 10–15 reps with elastic bands at RM-2 reps; 3 leg-exercises with 2 sets with 8 reps at RM-2 reps; IE-NS: 2 × 25 minutes, 8 isometric and dynamic strength exercises</td>
<td>Yes</td>
<td>60% JE-PS: 77%; IE-PNS: 42%</td>
<td>Wellness protocol. 4 × 10 week/18 months 1 × 60 minutes of mobility and flexibility exercise</td>
</tr>
<tr>
<td>Kemmler et al., 2015&lt;sup&gt;(26)&lt;/sup&gt;</td>
<td>JE/IE-PS, 16 years</td>
<td>Multi-component: high-impact aerobic dance,</td>
<td>In total 4 sessions/week; 2 × 60 minutes/week JE-S,</td>
<td></td>
<td>Yes</td>
<td>57% JE-PS: 83%; IE-PNS: 31%</td>
<td>No intervention</td>
</tr>
</tbody>
</table>

(Continues)
Table 2. Continued

<table>
<thead>
<tr>
<th>First author, year, reference</th>
<th>Focus of the intervention</th>
<th>Design, supervision length of intervention</th>
<th>Type of exercise in the EG: (supplementation with ca and vitamin D)</th>
<th>Exercise/strain composition</th>
<th>Progression of intensity</th>
<th>Attendance rate</th>
<th>Type of exercise/intervention in the CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korpelainen et al., 2006[27]</td>
<td>Bone strength and fall prevention</td>
<td>JE/JE-PNS, 30 months</td>
<td>Jumping, DRT, functional gymnastics, balance (last 4 years); up to 500 IU/d Vit D, 1000 mg Ca.</td>
<td>20 minutes of HI aerobic dance at 70–85% HRmax, 4 x 15 different jumps; periodized DRT 9–13 exercises up to 90% 1RM with periods of high velocity; IE-NS: 2 x 25 minutes, 8 isometric and dynamic strength exercises; 5–6 flexibility exercises</td>
<td>JE-S for 6 months/year: 1 x 60 minutes/week + 6 x 20 minutes IE-NS intermitted by IE-NS, 7 x 20 minutes/week; HI exercises, DRT in circuit mode ≥4 exercises, 3 sets of 30 seconds of exercise – 30 seconds of rest, focus on maximum reps/30 seconds, shorter version during IE-NS</td>
<td>Yes &lt;50% JE-PS: 75% IE-PNS: 43%</td>
<td>No physical intervention, social interaction, health information</td>
</tr>
<tr>
<td>Lamb et al., 2020[9]</td>
<td>Fall prevention</td>
<td>IE-PNS, 18 months</td>
<td>Multi-component: HI aerobic exercises, jumps, balance, DRT; no supplements</td>
<td>In total ≥3 x 30 minutes/week; 5 DRT-exercises with 4 intensity levels up to 2 sets of 10 reps; and 12 balance exercises with 4 levels; up to 4 sets of 10 steps; 2 x 30 minutes walking with habitual speed</td>
<td>No</td>
<td>n.g.</td>
<td>Advice by mail</td>
</tr>
<tr>
<td>Liu-Ambrose et al., 2019[28]</td>
<td>Fall prevention</td>
<td>IE-PNS, 12 months</td>
<td>OEP (see Iliffe et al., 2014); no supplements</td>
<td>In total ≥3 x 30 minutes/week; 5 DRT-exercises with up to 2 sets of 10 reps; and 12 balance exercises with up to 4 sets of 10 steps; 2 x 30 minutes walking with habitual speed + usual care (see control group)</td>
<td>No</td>
<td>DRT, B: 63% Walking: 127%</td>
<td>“Usual care”: evaluation (and treatment?) by a geriatrician at baseline and 6 and 12 months</td>
</tr>
<tr>
<td>McMurdoo et al., 1997[29]</td>
<td>Bone strength and fall prevention</td>
<td>JE-P(?), 24 months</td>
<td>Weight-bearing aerobic exercise to music; 1000 mg/d calcium</td>
<td>3 x 45 minutes/week for 3 x 10 weeks/year</td>
<td>No</td>
<td>76%</td>
<td>No physical intervention</td>
</tr>
</tbody>
</table>

(Continues)
<table>
<thead>
<tr>
<th>First author, year, reference</th>
<th>Focus of the intervention</th>
<th>Design, supervision length of intervention</th>
<th>Type of exercise in the EG: (supplementation with Ca and vitamin D)</th>
<th>Exercise/strain composition</th>
<th>Progression of intensity</th>
<th>Attendance rate</th>
<th>Type of exercise/intervention in the CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preisinger et al., 1996(30)</td>
<td>Bone strength and back pain</td>
<td>IE-PNS, 48 months</td>
<td>Physiotherapy including postural stability, motor control, coordination, functional DRT, flexibility; no supplements</td>
<td>≥3 × 20 minutes/week; resistance exercises with elastic bands on unstable surface/seat</td>
<td>No</td>
<td>n.a.⁵</td>
<td>No exercise intervention, partial massage, electrotherapy in EG and CG</td>
</tr>
<tr>
<td>Robertson et al., 2001, RCT(31)</td>
<td>Fall prevention</td>
<td>IE-PNS, 12 months</td>
<td>Multi-component: walking, DRT, balance; no supplements</td>
<td>In total ≥5 sessions/week; ≥3 × 30 minutes/week a set of muscle strengthening and balance retraining exercise (?) and ≥2 × week walking (?)</td>
<td>Yes</td>
<td>n.g.⁴</td>
<td>“Usual care” (study nurse visits)</td>
</tr>
<tr>
<td>Sakamoto et al., 2012(32)</td>
<td>Fall prevention</td>
<td>IE-PNS, 6 mon.</td>
<td>Balance; no supplements</td>
<td>7 × week, 3 sessions/ d × 60 seconds one-leg stand without holding on an object (when possible)</td>
<td>No</td>
<td>n.g.</td>
<td>No intervention</td>
</tr>
<tr>
<td>Karinkanta et al., 2009(33)</td>
<td></td>
<td>See Karinkanta 2007: 5-year FU after a 12-month intervention</td>
<td>No structured intervention during FU</td>
<td>No structured intervention during FU</td>
<td>No structured intervention during FU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korpelainen et al., 2010(34)</td>
<td></td>
<td>See Korpelainen 2006: 5-year FU after a 30-month intervention</td>
<td>No structured intervention during FU</td>
<td>No structured intervention during FU</td>
<td>No structured intervention during FU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinaki et al., 2002(35)</td>
<td>Bone strength</td>
<td>IE-PNS, 2 years</td>
<td>8-year FU of a 24-month lower back resistance exercise; no supplements</td>
<td>5 sessions/week, 1 set of 10 reps back extension in a lying prone position with backpacks; backpack weight 30% of the maximal back extensor strength (BES)</td>
<td>Yes</td>
<td>n.g.</td>
<td>No intervention during study and FU-period</td>
</tr>
</tbody>
</table>

Ca = calcium; DRT = dynamic resistance exercise; FAME = falls management exercise; FU = follow-up; IE = individual exercise (predominately home-based); JE = joint exercise (predominately facility-based); n.a. = not applicable; n.g. = not given; PNS = predominately non-supervised; PS = predominately supervised; OEP = Otago Exercise Program; RM = repetition maximum; RPE = rate of perceived exertion; s/w = sessions per week; vitamin D = cholecalciferol.

Shaded rows = studies on major osteoporotic fractures.

¹The exercise description and study aims (“bone and muscle health”) tend to suggest bone strength; however, the exercise program might also include fall reduction.

²70% of the participants did at least two sessions per week; 62% at least 3 sessions/week.

³Included were participants who exercised ≥3 × 20 min/week (44%).

⁴43% of the participants did three or more sessions; 72% at least 2 sessions/week.

⁵The Otago Exercise Program (OEP) conducted 7 supervised and led sessions over 6 months.
observed or reported fracture location, 44 hip fractures were recorded in the EG and 58 in the CG. Forearm and wrist fractures appeared 69 times in the exercise and 58 times in the CG. Finally, 29 vertebral fractures were recorded for the EG and 55 in the CG.

Meta-analysis results

Exercise effects on low-trauma overall fractures

The mixed-effects conditional Poisson regression revealed a significant ($p = 0.003$) effect of exercise on overall fractures (IR 0.67, 95% CI 0.51–0.87). This effect was confirmed by the Mantel–Haenszel model (IR 0.82, 95% CI 0.71–0.94). Heterogeneity between the trials ($I^2 = 40\%$) was moderate but nevertheless significant (Fig. 2A). In summary, we thus confirmed our hypothesis that exercise reduces the number of low-trauma overall fractures compared with a control group.

Exercise effects on major osteoporotic fractures

The mixed-effects conditional Poisson regression demonstrated a significant ($p = 0.011$) effect of exercise on major osteoporotic fractures (IR 0.69; 95% CI 0.52–0.92) (Fig. 2). This result was confirmed by the Mantel–Haenszel model (IR 0.70; 95% CI 0.56–0.86). Heterogeneity between the trials ($I^2 = 1\%$) was negligible. In summary, we confirmed our hypothesis that exercise reduces the number of major osteoporotic fractures compared with a control group.

Assessment of small study effects

The funnel plot suggests some evidence for publication/small study bias (Fig. 3A) on low-trauma overall fractures. Tendentially, moderate-size studies (ie, center area of the funnel plot) predominately supplied evidence for positive exercise effects on fracture reduction. However, the rank correlation test for funnel plot asymmetry did not indicate asymmetry ($p = 0.57$).

The funnel plot of the studies that reported major osteoporotic fracture data suggests only minor evidence for publication/small study bias (Fig. 3B). In parallel, the rank correlation test for funnel plot asymmetry did not indicate asymmetry ($p = 0.23$).

Subgroup analyses

Effects of supervision on exercise effects on low-trauma overall and major osteoporotic fractures

Classifying the studies according to their degree of supervision (Fig. 4), we observed differences for both low-trauma overall fractures ($p = 0.03$) and major osteoporotic fractures ($p = 0.004$). Relative risk on overall fracture in PS studies (IR 0.44; 95% CI 0.27–0.73) was nearly 50% lower compared with PNS trials (IR 0.83; 95% CI 0.60–1.14) (Fig. 4A). In parallel, we observed lower major osteoporotic fracture incidence ratios in PS (IR 0.38; 95% CI 0.19–0.76, Fig. 4B) compared with PNS (IR 0.82; 95% CI: 0.64–1.05) studies. In contrast to PS studies ($p \leq 0.006$), PNS exercise studies did not reduce the incidence ratio for low-trauma overall ($p = 0.240$) or major osteoporotic fractures ($p = 0.114$). Heterogeneity between the trials can be considered as negligible ($I^2 = 0\%$) to low ($I^2 = 27\%$) among the subgroups (ie, PS versus PNS) (Fig. 4A, B) independent of the fracture type (ie, overall versus major osteoporotic fractures). Thus, we clearly confirmed our hypothesis of superior effects of
<table>
<thead>
<tr>
<th>Author, year, reference</th>
<th>Eligibility criteria</th>
<th>Random allocation</th>
<th>Allocation concealment</th>
<th>Inter-group homogeneity</th>
<th>Blinding participants</th>
<th>Blinding personnel</th>
<th>Blinding assessors</th>
<th>Participation ≥85% allocation</th>
<th>Intention to treat analysis</th>
<th>Between-group comparison</th>
<th>Measure of variability</th>
<th>Total score PEDro</th>
<th>Adverse effects reported</th>
<th>Attendance reported</th>
<th>Activity monitoring in the CG</th>
<th>Relative exercise intensity constant</th>
<th>Exercise volume &amp; Energy expended</th>
<th>Total score TESTEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashburn et al., 2007(18)</td>
<td>Y</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bischoff-Ferrari et al., 2020(20)</td>
<td>Y</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan et al., 2004(19)</td>
<td>Y</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ebrahim et al., 1997(20)</td>
<td>Y</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gianouidis et al., 2014(21)</td>
<td>Y</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gill et al., 2016(22)</td>
<td>Y</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iliffe et al., 2014(23)</td>
<td>Y</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karlinka et al., 2007(24)</td>
<td>Y</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kemmler et al., 2010(25)</td>
<td>Y</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kemmler et al., 2015(26)</td>
<td>Y</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korpelainen et al., 2006(27)</td>
<td>Y</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamb et al., 2020(28)</td>
<td>Y</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu-Ambrose et al., 2019(29)</td>
<td>Y</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McMurdo et al., 1997(30)</td>
<td>Y</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preisinger et al., 1996(31)</td>
<td>Y</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continues)
### Table 3. Continued

| Author, year, reference | Eligibility criteria | Random allocation $^a$ | Allocation concealment | Inter-group homogeneity | Blinding participants | Blinding personnel | Blinding assessors | Participation $\geq85\%$ of to treat analysis $^b$ | Intention to treat analysis $^c$ | Between-group comparison | Measure of variability | Total score PEDro | Adverse effects reported | Attendance reported in the CG | Activity monitoring in the CG | Relative exercise intensity constant | Exercise volume & Energy expended | Total score TESTEX |
|------------------------|---------------------|------------------------|------------------------|-------------------------|----------------------|-------------------|------------------|------------------------|------------------------|------------------------|----------------------|----------------|------------------------|-------------------------------|-----------------|--------------------------|--------------------------|----------------|----------------|---|
| Robertson et al., 2001$^{(1)}$ | Y                   | +                      | –                      | –                       | –                    | +                 | –                | +                      | +                      | –                      | –                    | 4                | +                      | –                          | –               | –                       | –                       | –              | –              | 7 |
| Sakamoto et al., 2012$^{(2)}$ | Y                   | +                      | –                      | +                       | –                    | –                 | –                | –                      | –                      | +                      | +                    | 5                | –                      | –                          | –               | –                       | –                       | –              | –              | 6 |
| Sinaki et al., 2002$^{(3)}$ | Y                   | +                      | –                      | +                       | –                    | –                 | –                | –                      | –                      | +                      | +                    | 7                | –                      | –                          | –               | –                       | –                       | –              | –              | 7 |

Shaded rows = Studies on major osteoporotic fractures.
$^a$TESTEX awards one point for listing the eligibility criteria and also, in contrast to PEDro, a further point for the between-group comparison of at least one secondary outcome.
$^b$Studies that either have not randomly assigned participants to the groups (–) or retrospectively analyze for training frequency (n.a.).

In the present study, we provided evidence on low-trauma fractures and for the predominately supervised versus non-supervised exercise programs on low-trauma overall and major osteoporotic fractures. To the additional studies of Lamb and colleagues$^{(4)}$ with proven positive effects on fall reduction among generally non-supervised older adults, the present results on supervision, Fisher and colleagues$^{(5)}$ reported a less favorable exercise effect. This result can be widely related to the additional studies of Lamb and colleagues$^{(4)}$ reported comparably negligible effects for overall low-trauma and major osteoporotic fractures.

Discussion

Turning to the training aims and exercise strategy of the included trials, the majority of studies applied types of exercise predominantly focused on high-frequency training programs (resistance exercises for the exercise and active older adults (Fig. 2A)). Applying the Otago Exercise Programme$^{(6)}$ with proven positive effects for high-frequency training programs (Table 2), exercise protocols and resistance exercises for the control group (Table 2), reported and compared negligible effects for the long-term follow-up of the present study (Table 2). Finally, the additional studies of Lamb and colleagues$^{(4)}$ reported favorable results for the CG that were provided with concentrated on fall-related fractures (relative risk [RR] 0.74, 95% CI 0.51–0.92) was roughly comparable with two meta-analyses that were provided with a less favorable exercise effect. This result can be widely related to the additional studies of Lamb and colleagues$^{(4)}$ reported comparably negligible effects for overall low-trauma and major osteoporotic fractures.

In a recent meta-analysis on resistance training effects that concentrated on fall-related fractures (relative risk [RR] 0.74, 95% CI 0.51–0.92) was roughly comparable with two meta-analyses that were provided with a less favorable exercise effect. This result can be widely related to the additional studies of Lamb and colleagues$^{(4)}$ reported comparably negligible effects for overall low-trauma and major osteoporotic fractures.
Fig. 2. Forest plot of data on exercise effects on low-trauma overall fracture (A, upper graph) and major osteoporotic fracture (B, lower graph) incidence ratio. The data are shown as pooled relative risk (incidence [rate] ratio) with 95% confidence interval (CI) for overall fracture rate in the exercise versus control group. EG = exercise group; CG = control group; yrs = participant years; frs = fractures.
or training contents that exclusively or predominately focus on fall prevention (Table 2). Only a few studies11,19,24,30,35 applied dedicated bone-strengthening protocols. There is an ongoing discussion as to which training aim/strategy is more promising in fracture reduction.50 Although it is important to define quantifiable objectives in the training process, we feel that this debate is a rather academic issue. Applying state-of-the-art training science allows multiple training aims to be addressed with the same, albeit slightly adapted, training content.51 Beyond general training strategy, the failure to properly respect basic principles of training science (eg, progression, individualization, variation) is a methodological weakness of many trials (Table 2). Apart from the (direct) negative effect of less sophisticated exercise programs on meta-analyses results, another aspect has to be considered: In contrast to methodologic quality,16,17,33 there is still no recognized score available for determining the quality of the exercise intervention and thus enable appropriate weighting of the studies. Both features definitely represent a major limitation of meta-analysis in the area of exercise52,54 and hinder the achievement of higher exercise effects.54

At this point, we would like to briefly address limitations and/or particularities of the present work. (i) Although we excluded studies that reported fractures caused by high trauma (eg, car or bicycle accidents, falls from levels higher than standing), we might have failed to include “low-trauma fractures” only in some cases. (ii) In contrast to FRAX13 we included all types of vertebral and humerus fractures in the analysis. (iii) Because of the focus on fall-related or non-vertebral fractures in 12 of 20 studies,9,10,18,22-25,27-31 the contribution of vertebral fractures to major osteoporotic fractures was low. (iv) We included trials with physically active control groups,10,20,25 massage/electrotherapy (“when needed”),11 usual care/nurse contact,18,20,28,31 or information/health education/advice by email9,21,22,27. However, we feel that the corresponding effects on fracture reduction are negligible to low. More important might be the failure of most studies to monitor exercise/physical activity in the CG (Table 3) and the resulting inability to exclude changes of exercise/physical activity with impact on bone strength and/or falls. (v) After intense internal discussions, we also included a study that focused on Parkinson’s disease (PD) patients. One may argue that the pathologic status of PD might decrease the exercise effect on falls (and thus fractures); however, there is no evidence that exercise effects on bone strength were limited in PD patients. (vi) We included one study (or more precisely, intervention) <6 months in duration.18 We agree that such a period is too short to reach the full amount of mineralized bone55,56 at least when accepting bone remodeling as the primary mode of bone renewal in adults. However, this argument does not apply for the exercise programs focusing on fall reduction, which the 6-week intervention of Ashburn and colleagues19 addressed. (vii) We excluded three studies14,35,58 from the sub-analysis on supervision effects because of the fact that the relevance of supervision might be negligible 5 to 8 years after the end of the intervention. However, including these studies in the analysis did not considerably affect the result. In this context, it is recognizable that the FU studies provided evidence for a sustaining effect of exercise years after the dedicated intervention. In summary, the present systematic review and meta-analysis provided evidence for positive effects of exercise on low-trauma overall and major osteoporotic fractures in adults. Considering the importance of supervision of the exercise program, online formats with supervised virtual training might enhance the effectiveness of home-based exercise programs for older adults.

**Disclosures**

The authors declare that they have no conflicts of interest relevant for the present systematic review and meta-analysis. No sources of funding were applied for the preparation of this article.

**Acknowledgments**

We thank the Elisabeth-Bonhoff Stiftung, Berlin, Germany, for funding the national guideline on “exercise and fracture prevention” initiated by the Dachverband Osteologie (DVO) e.V. We also thank all the authors who have provided missing information needed for the present work. The article was performed in (partial) fulfillment of the requirements for IH’s obtaining the degree Dr. med. Dent.
Fig. 4. Forest plot of differences on exercise supervision on low-trauma overall (A, upper graph) and major osteoporotic fracture (B, lower graph) incidence ratio. The data are shown as pooled relative risk (incidence [rate] ratio) with 95% confidence intervals (CI) for overall fracture rate in the exercise versus control group. EG = exercise group; CG = control group; yrs = participant years; frs = fractures.
The present systematic review and meta-analysis does not contain data or description of individual human or animal patients.

Authors’ roles: All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data of this systematic review and meta-analysis. All authors drafted and revised the manuscript. Article search, screening, data extraction, and rating was performed by IH, MS, MK, SVS, DS, and WK. Formal analysis was conducted by MK. All authors read the final version of the manuscript and agree to be accountable for all aspects of the work. Open Access funding enabled and organized by Projekt DEAL.

Author Contributions

Isabelle Hoffmann: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision; validation; writing – original draft; writing – review and editing. Mahdieh Shojaa: Conceptualization; data curation; investigation; methodology; validation; writing – original draft; writing – review and editing. Matthias Kohl: Conceptualization; data curation; formal analysis; investigation; methodology; software; validation; writing – original draft; writing – review and editing. Simon von Stengel: Conceptualization; data curation; investigation; methodology; project administration; resources; validation; writing – original draft; writing – review and editing. Matthias Kohl: Conceptualization; data curation; investigation; methodology; software; validation; writing – original draft; writing – review and editing. Matthias Kohl: Conceptualization; data curation; formal analysis; investigation; methodology; software; validation; writing – original draft; writing – review and editing.

Bernd Kladny: Conceptualization; methodology; validation; writing – original draft; writing – review and editing. Katharina Kerschan-Schindl: Conceptualization; investigation; methodology; project administration; validation; writing – original draft; writing – review and editing. Verena Krupp: Conceptualization; investigation; methodology; project administration; validation; writing – original draft; writing – review and editing. Markus Goeschl: Conceptualization; funding acquisition; investigation; methodology; resources; validation; writing – original draft; writing – review and editing. Jakob Stampfl: Conceptualization; methodology; validation; writing – original draft; writing – review and editing. Stefan Middeldorf: Conceptualization; investigation; methodology; validation; writing – original draft; writing – review and editing. Katharina Kerschan-Schindl: Conceptualization; investigation; methodology; project administration; validation; writing – original draft; writing – review and editing. Bernd Kladny: Conceptualization; investigation; methodology; supervision; validation; writing – original draft; writing – review and editing. Jürgen Clausen: Conceptualization; methodology; supervision; validation; writing – original draft; writing – review and editing. Uwe Lange: Conceptualization; investigation; methodology; validation; writing – original draft; writing – review and editing. Stefan Middeldorf: Conceptualization; investigation; methodology; validation; writing – original draft; writing – review and editing. Stefan Peters: Conceptualization; investigation; methodology; validation; writing – original draft; writing – review and editing. Daniel Schoene: Conceptualization; investigation; methodology; resources; validation; writing – original draft; writing – review and editing. Cornel Sieber: Conceptualization; investigation; methodology; resources; validation; writing – original draft; writing – review and editing. Reina Tholen: Conceptualization; investigation; methodology; supervision; validation; writing – original draft; writing – review and editing. Friederike Thomasius: Conceptualization; funding acquisition; investigation; methodology; supervision; validation; writing – original draft; writing – review and editing. Heike A. Bischoff-Ferrari: Data curation; formal analysis; methodology; resources; supervision; validation; writing – original draft; writing – review and editing. Michael Uder: Conceptualization; data curation; investigation; methodology; project administration; resources; supervision; validation; writing – original draft; writing – review and editing. Wolfgang Kemmler: Conceptualization; data curation; funding acquisition; investigation; methodology; project administration; resources; supervision; validation; writing – original draft; writing – review and editing.

Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1002/jbmr.4683.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author (WK) upon reasonable request.

References

 programme to reduce the risk of falling among people with Parkinson’s disease. J Neurol Neurosurg Psychiatry. 2007;78:678-684.


29. McMurdo ME, Moyle PA, Paterson CR. Controlled trial of weight bearing exercise in older women in relation to bone density and falls. BMJ. 1997;314:569.


56. Erben RG. Hypothesis: coupling between resorption and formation in cancellous bone remodeling is a mechanically controlled event. J Bone and Mineral Research. 2022; 11. Downloaded from https://asbmr.onlinelibrary.wiley.com/doi/10.1002/jbmr.4683 by Hochschule Furtwangen University Library for personal use; OA articles are governed by the applicable Creative Commons License.