Review Article

Adverse events and safety issues associated with physical activity and exercise for adults with osteoporosis and osteopenia: A systematic review of observational studies and an updated review of interventional studies

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Abstract

Objectives: We conducted a systematic review to identify adverse effects of physical activity and/or exercise for adults with osteoporosis/osteopenia. We synthesised evidence from observational studies, and updated three previously published systematic reviews. **Methods:** We searched MEDLINE, EMBASE, CINAHL, Web of Science, grey literature and reference lists of relevant studies. Selection criteria were: (1) observational studies in patients with osteoporosis/osteopenia; and (2) in accordance with the criteria used in the previous reviews. A narrative synthesis was conducted for the observational data. Random effects meta-analysis was undertaken for the review updates. **Results:** For the observational synthesis 14 studies were included. The majority of studies reported no adverse events, reduced incidence/improvement, or no significant change after physical activity or exercise. Activities that involved spinal flexion (certain yoga moves and sit-ups) were associated with a greater risk of vertebral fractures but these events were rare. For the update of reviews, 57 additional studies were identified. Exercise was generally associated with a greater number of minor adverse events including mild muscle/joint pain. Serious adverse events were rare and could not be attributed to the intervention. **Conclusion:** Patients with osteoporosis/osteopenia can safely participate in structured exercise programmes, whether at home or in supervised facilities. **Systematic review registration for observational studies:** PROSPERO 2017: CRD42017070551

Keywords: Osteoporosis, Physical activity, Exercise, Adverse events, Systematic review

Introduction

Osteoporosis is one of the most common diseases to affect older people. With the ageing of the population worldwide, the numbers are expected to increase[1], and by the year 2025 it has been estimated that more than 30 million men and women aged 65 and older will be affected in the European Union alone[2]. It has been predicted that 40% of these women and 15-30% of men will develop at least one fragility fracture during their remaining lifetime[3,4]. Osteoporosis is a serious public health burden. Fragility fractures are associated with significant morbidity, mortality,

decreased quality of life, and are a burden on health systems[5].

In the management of osteoporosis, pharmacological therapy, as well as advice on healthy living, is commonly provided to patients[6,7]; there is also an emphasis on maintaining or increasing physical activity and exercise to improve bone health and reduce falls. Given the substantially increased risk of falls and fractures in patients with osteoporosis (patients with osteoporosis tend to be women, elderly, frail, and have an increased risk of falls and fractures due to bone fragility), healthcare professionals, as well as the patients themselves, often question the safety of physical activity and exercise. Indeed, exercise programmes for such patients should be safe as well as sustainable. It is well established that physical activity, particularly weight-bearing exercise, is beneficial in preventing bone fractures and falls in individuals with low bone density, as well as in the prevention of osteoporosis[8-11]. However, providing accurate advice on safety and adverse effects of physical activity and exercise in patients with osteoporosis is hampered by limited data on adverse events and inconsistencies in the literature.

Three systematic reviews of interventional studies of exercise for adults with osteoporosis, treatment or prevention of osteoporosis and prevention of falls in older people[12-14] have been undertaken. However, there is lack of a comprehensive synthesis of the observational and non-randomised literature on the safety and adverse effects of physical activity or exercise in adults with osteoporosis, apart from two consensus statements[15,16].

In this context, using systematic review methodology, we aimed to identify evidence on specific adverse effects of physical activity and/or exercise in adults with osteoporosis or osteopenia. To do this we have carried out a systematic review of observational or non-randomised studies. The first objective was to assess the characteristics of people with osteoporosis or osteopenia who experience adverse events after physical activity and/or exercise. A second objective was to ascertain the specific exercises or movements within the activities that led to the adverse events. In addition, we assessed the various types of adverse events experienced after physical activity and/or exercise in people with osteoporosis or osteopenia. We also sought to identify any gaps in the available literature. Finally, given the publication of several interventional studies on the topic since 2011-16 covering exercise in people with osteoporosis, osteopenia or at risk of falls, we have updated the three published systematic reviews with a specific focus on adverse events.

Methods

(a) Observational and non-randomised studies

Data sources and search strategy: observational and non-randomised studies

We conducted the observational review using a predefined protocol, registered in the PROSPERO prospective register of systematic reviews (CRD42017070551). All reviews were carried out in accordance with PRISMA guidelines[17] (Appendix 1). Observational (prospective cohort, nested case-control, or case-control, retrospective cohort) studies, case reports, case studies, and non-RCTs which have reported on adverse events and safety issues associated with physical activity and/or exercise in patients with osteoporosis, were searched in MEDLINE, EMBASE, and CINAHL databases from inception to 27 June 2017. The computer-based searches combined free and MeSH search terms and combination of key words related to the exposures/interventions (e.g., "physical activity", "exercise") and outcomes (e.g., "adverse events", "fractures", "injuries") and population (e.g., "osteoporosis", "fragility fracture") with no restrictions on language. The MEDLINE search strategy was adapted to the other databases using the appropriate controlled vocabulary. Reference lists of relevant articles such as reviews were manually scanned for additional studies likely to have been missed by the electronic search. Finally, we searched the ISI Web of Science for papers which cited the studies initially included in the review. Details on the MEDLINE search strategy are provided in Appendix 2.

Eligibility criteria

Studies were eligible if: (i) they were conducted in adults with osteoporosis or osteopenia; and (ii) they employed physical activity and/or exercise, either as a healthcare intervention or as a lifestyle choice. Adverse events were defined as any events the authors described as 'adverse'. To ensure all relevant studies were included, no criteria were included to describe the definition of adverse events.

Data extraction and quality assessment

The initial screening of titles and abstracts to retrieve potentially relevant articles was performed by one reviewer (S.K.K.). Detailed evaluation of the full texts of these relevant articles was conducted to determine whether they met all inclusion criteria and this was conducted independently by two reviewers (S.K.K. and E.C.). If necessary, disagreements and uncertainties over inclusion/exclusion of an article were resolved by discussion with a third reviewer (S.L.). A standardized predesigned data collection form was used for data extraction. Data were extracted, where available, on study publication date, study design, geographical location, baseline age, percentage of females, duration of follow-up, sample size, type of exercise or physical activity, frequency and duration of activity, type of adverse events, and risk estimates where relevant. For non-randomised studies including cohort and case-control studies, methodological quality was assessed based on the nine-point Newcastle–Ottawa Scale (NOS)[18]. It uses three pre-defined domains namely: selection of participants (population representativeness), comparability (adjustment for confounders), and ascertainment of outcomes of interest. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Nine

points on the NOS reflects the highest study quality. A score of ≥5 indicates adequate methodological quality.

Data synthesis and analysis

It was not possible to calculate summary measures or average effects across studies given the diversity of the intervention designs and study methods and the heterogeneous nature of the outcome measures. Effective comparisons could also not be made across studies because of the heterogeneity of the data. The findings of each relevant included study were summarized in tables that included the main characteristics of the study and the results in natural units as reported by the investigators. A narrative synthesis with separate results from each study was also performed. For the above reasons, it was not possible to conduct subgroup and sensitivity analyses.

(b) Updated systematic review of interventional evidence

We took a pragmatic decision to undertake a systematic review to update these three already published reviews[12-14] rather than carry out a new complete review ourselves. To identify all studies published since the systematic reviews, trials were selected in accordance with the exclusion and inclusion criteria used in the previous reviews. Databases searched were synonymous with those searched in the previous reviews in order to replicate the methodology to the highest degree possible. Two authors independently screened the searches, and independently assessed full-text articles for those with potential eligibility and resolved disagreement through discussion (SK and EC for the observational data; JW and LJ for the updated Sherrington review[12]; JW and MC for the updated Howe review[13]; JW and NG for the updated Giangregorio review[14]). One author (either MC, LJ or NG) extracted data on adverse events from the new eligible trials plus all the trials included in the previous reviews using a self-made data extraction form. Adverse events were reported as the number of participants reporting adverse events. Data were collected for serious adverse events, the total adverse events reported, the adverse events that were attributable to the exercise or control group, and finally the general adverse events reported. In trials that reported data on adverse events for both control and intervention participants, adverse event rates were pooled and analysed using random-effects meta-analysis using the 'metan' command in Stata (StataCorp 2011, Release 12). Where possible, all reported adverse events were calculated as incidence per person years using the number of adverse events divided by the number of participants in the study arm and the reported follow up time.

Results: observational and non-randomised data

Study identification and selection

The Figure 1 shows the flow of studies through the review. The initial search of relevant databases and manual scanning of reference lists of relevant studies identified 1,013 potentially relevant citations. After the initial screening which was based on titles and abstracts, 32 articles remained for full text evaluation. Following detailed evaluation, 18 articles were excluded because: (i) they included populations not relevant to review (n=7); (ii) adverse event outcomes were not reported (n=5); and (iii) study designs were not relevant to review e.g. were randomised controlled trials (n=6). The remaining 14 articles comprising 13 unique studies met the inclusion criteria and were included in the review[19-32].

Study characteristics and quality

Table 1 summarizes the characteristics of the studies included in the review. Studies were published between 1984 and 2016. Two articles were based on findings from the same study[20,21], but the recent publication was based on 5-year follow-up findings. The majority of studies were conducted in North America (USA and Canada), with five conducted in Europe (Norway, Sweden, Austria, Turkey, and Croatia), and two conducted in Asia (Japan and Korea). Except for three case reports[27-29], all studies utilised observational cohort designs. The majority of the study designs had multiple intervention groups which were non-randomised, while four used before and after designs[25,26,31,32]. Methodological quality of included observational cohort studies using Newcastle–Ottawa Scale criteria ranged from 3-6 (Table 1).

Baseline characteristics of study populations evaluated

Sample size of cohorts (excluding case reports) ranged from 26 to 741 participants (Table 1). Overall, the 14 studies involved 1,226 participants. Lu and colleagues[32], included men but the majority of studies included only female participants. Patients were recruited from diverse sources and these included healthcare settings, the community, referral from physicians, population databases, and the media (newspaper, radio, poster advertisements, as well as the internet). Baseline age of study participants ranged from 36 years and above and duration of follow-up, where follow-up occurred, ranged from 4 weeks to 9.7 years. Except for one study (findings reported in two articles[20,21]), all studies (excluding the case reports) had exclusion criteria for recruiting participants and these included history of chronic diseases, health problems or neurological conditions that might impair physical activity or exercise and secondary osteoporosis.

Types of physical activity and/or exercise undertaken

Table 2 provides types of interventions (physical activity and/or exercise) utilized in eligible studies, frequency and duration of interventions, as well as the population groups evaluated in these studies. There were several diverse types of physical activity or exercise and these included spinal extension and flexion exercises; use of free weights; aerobic exercises (walking, jogging, dance routines, exercise bicycles); balance exercises, stretching; Tai Chi; yoga; golfing;
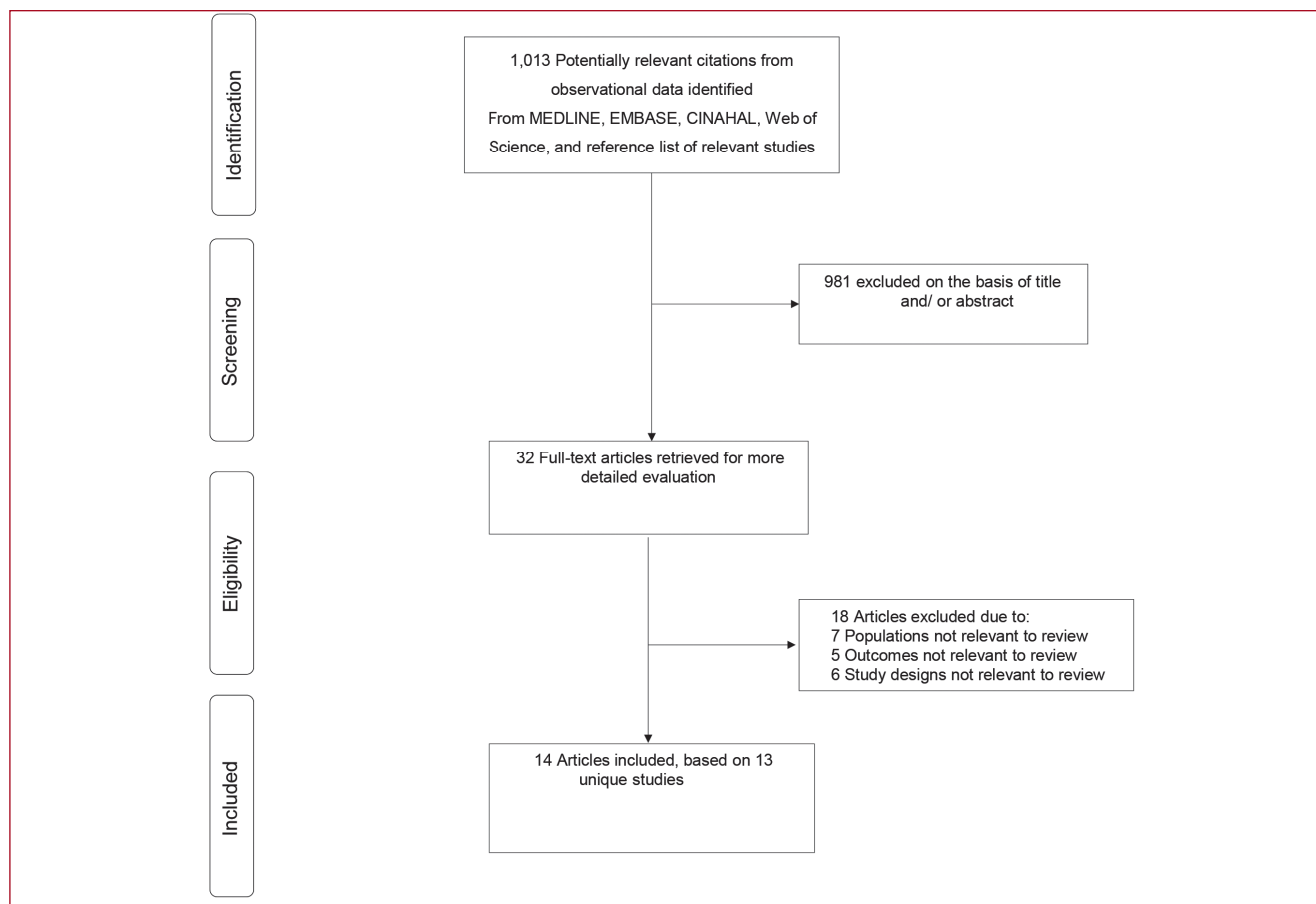
Figure 1. Selection of studies included in the review of observational studies.

as well as horseback riding. The majority of studies adopted the intervention/exercise activity as a programme which involved a combination of various exercise routines including warmup exercises. Yamazaki and colleagues utilized an exercise programme which only consisted of daily outdoor walking, after each participant had learned to walk at a speed that corresponded to their target heart rate using an exercise treadmill[24]. In the study of Tai Chi, a typical session involved stretching exercises, sequential movements of the limbs, and controlled breathing[25]. Lu and colleagues employed a yoga regimen consisting of 12 common poses specifically chosen for their safety, which concentrated on three common fracture sites – spine, hip, and femur, and avoided forward flexion-type exercises[32]. The exercise programmes were either facility based or home-based and were supervised or unsupervised after initial instructions had been provided. For some unsupervised groups, this was after patients had undergone a period of supervised exercise classes[20,22,24]. One study utilized an exercise programme combined with a patient education programme[26]. The frequency of physical activity or exercise sessions ranged from once a week to about four times a week and total duration ranged from 4 weeks to 12 years. The majority of studies used 2-3 intervention groups.

There were three case reports of adverse events during unstructured or unsupervised physical activities. One presented clinical findings of two women with low bone mineral density (BMD) after participation in horseback riding[27]. Another reported findings of three patients with osteopenia after they had participated in strenuous yoga flexion exercises[28]. The third case report presents post-golfing clinical findings in three healthy, active, postmenopausal patients with osteoporosis[29].

Adverse events experienced with physical activity and/ or exercise

In addition to outcomes such as bone mineral density, circulating blood bone markers, functional strength, and neuromuscular performance; adverse events evaluated by included studies were fractures, back pain, falls, joint pain, balance problems, mobility, quality of life, muscle soreness, and injuries. These were assessed by a variety of measures across studies, but were most often unexplained.

Table 1. Summary characteristics of studies included in the review.

Lead author, publication date	Location	Baseline year	Study design	Further details on study design	Population	Population source	Exclusion criteria	Age range (years)	Females (%)	Sample size	Drop-out rate	Duration of follow-up	Study quality
Sinaki, 1984	USA	1969-1981	Prospective cohort	Nonrandomised design with multiple intervention groups	Postmenopausal women with spinal osteoporosis and back pain	Healthcare setting	History of cancer, metabolic bone disease, secondary osteoporosis, and major health problems that could cause difficulty with compliance of exercise programmes	49-60	100	59	NR	1-6 years	6
Ekin, 1993	USA	N/A	Case report	N/A	Three postmenopausal women with osteoporosis who were healthy, active, and long-term golfers	Healthcare setting	N/A	63; 58; and 66 years respectively	3 women	3	N/A	N/A	N/A
Harrison, 1993	Canada	1983	Prospective cohort	Nonrandomised design with multiple intervention groups	Postmenopausal women with osteoporosis	Referred from physicians	NR	64.0*	100	139	78 remained at 4-year follow-up	4 years	5
Walker, 2000	Canada	1983	Retrospective cohort	Nonrandomised design with multiple intervention groups	Postmenopausal women with osteoporosis	Referred from physicians	NR	NR	100	89	NR	5 years	5
Kerschan-Schindl, 2000	Austria	NR	Prospective cohort	Nonrandomised design with intervention plus control group	Women with a history of postmenopausal fractures and an age-adjusted low bone mass	Healthcare setting	Smoking, secondary osteoporosis, neurologic disease, and any chronic disease other than osteoporosis	45-75	100	33	25 with complete data at end of study	9.7 years	5
Liu-Ambrose, 2004	Canada	NR	Prospective cohort	Groups assigned intervention on the basis of 'sway' measures	Women with low bone mass	Population databases as well as media (newspaper, radio, poster advertisements)	Women living in care facilities, of non-Caucasian race, regularly exercising twice weekly or more, had a history of illness or a condition for which exercise may cause adverse effects, had a history of illness or a condition that would affect balance (i.e. stroke and Parkinson's disease), or had a MMSE score of ≤ 23.	75-85	100	98	NR	13 weeks	5
Yamazaki, 2004	Japan	1999-2000	Prospective cohort	Nonrandomised design with intervention plus control group	Postmenopausal women with osteopenia/osteoporosis	Healthcare setting	History of oestrogen replacement therapy or had ever taken medication that affects bone metabolism, past or current smokers, history of cardiopulmonary disease or severe osteoarthritis and osteopathy that might have affected physical activity, participated in a sporting activity with a frequency of one or more times a week for at least the previous 5 years	49-75	100	50	27 subjects in the exercise group and 15 in the control group completed the study	12 months	5

Table 1. *(cont. from previous page).*

Lead author, publication date	Location	Baseline year	Study design	Further details on study design	Population	Population source	Exclusion criteria	Age range (years)	Females (%)	Sample size	Drop-out rate	Duration of follow-up	Study quality
Murphy, 2008	USA	NR	Prospective cohort	Before and after design	Community-dwelling women with or at risk for developing osteoporosis	Community dwellers	Involved in any Tai Chi within the past 12 months, required use of an assistive device or lower extremity orthosis to ambulate independently, history of neurological impairment or neuromuscular disease, had persistent pain >7/10 on a 0–10 pain scale, scored <20/30 on the MMSE, scored worse than 20/40 on the Snellen Chart with corrective lenses, or had their primary care provider identify a medical condition not identified during the screening process that would increase their fall risk or jeopardize their health by participating in the study.	55-80	100	42	31 completed the study	12 months	4
Tuzun, 2010	Turkey	NR	Prospective cohort	Observational cohort with a quasi-randomised element (divided into groups)	Postmenopausal women with osteoporosis	Healthcare setting	Systemic or psychiatric disorders and abnormal laboratory values	55-85	100	26	NR	12 weeks	6
Sinaki, 2013	USA	N/A	Case report of 3 cases	N/A	Three cases of women with osteopenia	Healthcare setting	N/A	87; 61; and 70 years	3 women	3	N/A	N/A	N/A
Cesarec, 2014	Croatia	NR	Prospective cohort	Before and after design	Women with osteopenia or osteoporosis	Healthcare setting	NR	36-84	100	39	NR	4 weeks	3
Hakestad, 2015	Norway	NR	Prospective cohort	Before and after design	Postmenopausal women with osteopenia and a healed forearm fracture	Healthcare setting - were part of an ongoing randomised controlled trial	History of hip or vertebral fracture, more than 3 osteoporotic fractures, medical conditions precluding active rehabilitation, already performing moderate to intense physical activity for more than 4 hours per week, inability to understand written or spoken Norwegian.	> 50	100	42	Complete data available for 31 participants	1 year	4
Lu, 2016	USA	2005	Prospective cohort	Before and after design	Majority of patients with osteoporosis or osteopenia	Internet recruited volunteers	Abnormal values on tests of circulating biomarkers, metabolic or bone disease	68.2*	Of 227 compliant patients, 202 were female	741	227 were compliant	2 years	4
Oh, 2016	Korea	N/A	Case report of 2 cases	N/A	Two cases of women with low bone mineral density	Healthcare setting	N/A	44 and 49 years	2 women	2	N/A	N/A	N/A

*, are mean/median ages; N/A, not applicable; NR, not reported; MSSE, Mini Mental State Exam

Table 2. Key characteristics of physical activity and/or exercises interventions included in review.

Lead author, publication date	Population	Type of physical activity or exercise	Frequency of physical activity or exercise program	Total duration of physical activity or exercise	Intervention groups	Adverse outcome measures assessed	Baseline status prior to study entry	Reported findings	Study conclusions
Sinaki, 1984	Postmenopausal women with spinal osteoporosis and back pain	Spinal extension and flexion exercises. Extension exercises consisted of exercises to strengthen erector muscles of the spine. Flexion exercises consisted of exercises that involved abdominal muscles, such as sit ups. All the treatment programmes included infrared heat and massage. Supervised exercise programme	NR	1-6 years	Extension (n=25); Flexion (n=9); Combined (extension plus flexion) (n=19); No exercise (n=6)	Wedging and compression fractures	NR	Fracture rate: Extension (16%); Flexion (89%); Combined (53%); Occurrence of fractures is significantly higher in flexion group compared with extension group	Spinal extension or isometric exercises more appropriate for patients with postmenopausal osteoporosis
Ekin, 1993	Three postmenopausal women with osteoporosis who were healthy, active, and long-term golfers	Golfing	NR	Were long-term golfers	N/A	Back pain and vertebral compression fractures	Were healthy, active, and long-term golfers	Severe back pain and vertebral compression fractures	The safety of golfing in women with osteoporosis is an issue. In the absence of robust evidence from RCTs, golfers with osteoporosis should wear rigid back support
Harrison, 1993	Postmenopausal women with osteoporosis	The exercise program consisted of a 20-minute low load, strength training session and 30 minutes of aerobic activities. Major muscle groups of the upper and lower extremities were strengthened using free weights. The patients performed 10 repetitions for each muscle group. Aerobic exercises consisted of walking and various aerobic 'dancercize' routines, choreographed to music. Supervised and unsupervised exercise programme	Twice a week	4 years	Supervised exercise group (n=36); Independent exercise group (n=37); Refused follow-up testing (n=5) After the exercise program, patients were grouped by improvement in fitness Group 1 – Least improvement in fitness Group 2 – Greatest improvement in fitness	Back pain and new fractures	There was no significant difference in initial level of fitness between the independent exercise group and the supervised exercise group. 44/78 patients had vertebral fractures and 45 had a total of 86 non-vertebral fractures. About 18 patients had back pain.	There was no significant difference in degree of improvement in fitness between the independent exercise group and the supervised exercise group. Overall, there was no significant improvement in back pain and there was an increase in vertebral and non-vertebral fractures at follow-up after the exercise programme. Compared with the group who experienced the least improvement in fitness, the group who experienced the greatest improvement in fitness had fewer vertebral fractures and less back pain (though not statistically significant).	Majority of patients in exercise programme found it to be of sufficient benefit. With encouragement from other osteoporotic patients, they are able to carry out more vigorous exercises without pain.
Walker, 2000	Postmenopausal women with osteoporosis	The exercise programme consisted of a 20-minute low load, strength training session and 30 minutes of aerobic activities. Major muscle groups of the upper and lower extremities were strengthened using free weights. The patients performed 10 repetitions for each muscle group. Aerobic exercises consisted of walking and various aerobic 'dancercize' routines, choreographed to music. Supervised and unsupervised exercise programme	Twice a week	5 years	Supervised (n=42) and unsupervised groups (n=47)	Incidence of fracture and loss of height	At study entry, 11 subjects in each group reported having had at least one fracture in the previous 12 months.	The incidence of fractures was reduced over the course of the study period. At study entry, 11 subjects in each group reported having had at least one fracture in the previous 12 months, while 2 in each group reported having had a fracture over the 5-year period.	Patients received a significant benefit as a result of their participation in the exercise program, irrespective of whether they exercised in a supervised program or in an unsupervised environment.

Table 2. *(cont. from previous page).*

| Lead author, publication date	Population	Type of physical activity or exercise	Frequency of physical activity or exercise program	Total duration of physical activity or exercise	Intervention groups	Adverse outcome measures assessed	Baseline status prior to study entry	Reported findings	Study conclusions
Kerschan-Schindl, 2000	Women with a history of postmenopausal fractures and an age-adjusted low bone mass	Home exercise programme. Included a warm-up period (brisk walking, modest jogging, etc), stretching exercises (hamstring, gastrocnemius, iliopsoas, pectoralis, and external rotation muscles of the hips), and movement patterns directed towards improving posture and coordination. Apart of the exercise program consisted of exercises with big gymnastic balls. During the initial phase, the exercises were supervised 20 times by a physical therapist. At half-yearly intervals, the subjects had an opportunity to participate in five supervised training sessions of exercise for reinforcement and correction of poor technique. Home exercise programme (supervised during the initial phase and at half-yearly intervals)	Training on a regular basis at home, at least three times a week for 20 min.	7 to 12 years	Exercise (n=19) and Control group (n=6)	Fracture rates, episodes of falling, neuromuscular performance	Persons with non-vertebral fractures: Exercise group – 15 (79%) Control group – 4 (67%) Persons with vertebral fractures: Exercise group – 9 (48%) Control group – 2 (33%)	No differences between groups in terms of fracture rates, falling episodes, and neuromuscular performance were observed. Persons with at least one non-vertebral fracture: Exercise group – 9 (47%) Control group – 3 (50%) Persons with at least one vertebral fracture: Exercise group – 6 Control group – 0	A home exercise program does not affect the outcome of postmenopausal women at high risk of fracture
Liu-Ambrose, 2004	Women with low bone mass	Resistance training – progressive and high-intensity in nature with the aims of increasing muscle strength in the extremities. Agility training – aims were to challenge hand-eye coordination, foot-eye coordination, dynamic balance, static balance and psychomotor performance (reaction time). Involved ball games, relay races, dance movements, and obstacle courses. Stretching - consisted of stretching exercises, deep breathing and relaxation techniques, and general posture education Supervised exercise programme	50-minute exercise classes twice weekly	13 weeks	Resistance training (n=32); Agility training (n=34), and Stretching (sham) exercises (n=32).	Relationship between change in balance confidence, and the changes in fall risk and physical abilities	Balance Confidence: mean (SD) Resistance – 76.3 (22.7) Agility – 78.3 (14.5) Stretching – 75.6 (23.7) Fall Risk Score: mean (SD) Resistance – 2.22 (0.70) Agility – 2.40 (0.86) Stretching – 1.92 (0.83)	Improvement in balance confidence which did not significantly correlate with changes in fall risk score, physical activity level, and physical abilities. Baseline balance confidence was not significantly different between the three groups. Balance Confidence: mean (SD) Resistance – 80.9 (17.1) Agility – 83.2 (12.2) Stretching – 76.3 (17.6) Fall Risk Score: mean (SD) Resistance – 1.39 (0.98) Agility – 1.49 (0.97) Stretching – 1.50 (0.95)	Both resistance training and agility training significantly improved balance confidence in community-dwelling older women with low bone mass after 13 weeks of participation.
Yamazaki, 2004	Postmenopausal women with osteopenia/osteoporosis	Daily outdoor walking at moderate intensity Home exercise programme (supervised during initial phase)	At least 1 hr duration with more than 8000 steps, at a frequency of 4 days per week	12 months	Exercise programme (n=32) and controls (n=18)	Fractures	None of the subjects revealed any evidence of thoracic or lumbar vertebral fractures	None of the subjects suffered any fractures during study period	Authors noted that the sample size was too small and study period was too short to detect the effect of exercise on the risk of vertebral fracture

Table 2. *(cont. from previous page).*

Lead author, publication date	Population	Type of physical activity or exercise	Frequency of physical activity or exercise program	Total duration of physical activity or exercise	Intervention groups	Adverse outcome measures assessed	Baseline status prior to study entry	Reported findings	Study conclusions
Murphy, 2008	Community-dwelling women with or at risk for developing osteoporosis	5-Form, Yang Style Tai Chi (TC) Supervised exercise programme	TC sessions twice a week, with self-practice at least 1 day per week. A typical session lasted 60–90 minutes and consisted of 10–20 minutes of warm-up, 45–60 minutes of TC practice, and approximately 7 minutes of cool-down activity	12 weeks	Before and after design	Balance confidence, balance performance, functional strength, mobility, and incidence of falls	Number of falls that occurred during a 12-month time interval preintervention - 27	TC significantly improved balance performance, functional strength, and functional mobility immediately postintervention. All improvements, except for balance on the right leg, were sustained at the 6-month follow-up. But only improvements in functional strength and mobility remained evident at the 12-month follow-up. There was no significant change in falls incidence Number of falls recorded during 12-months postintervention - 27	Five-Form, Yang Style TC appears to be a safe and relatively low-cost exercise intervention that can enhance balance, functional strength, and mobility among an older group of independent, community-dwelling females.
Tuzun, 2010	Postmenopausal women with osteoporosis	Yoga programme (combination of breathing and movement) and classical osteoporosis exercise program (involved strengthening and stretching exercises of the abdominal, back, quadriceps and hamstring muscles, balance and posture exercises Supervised exercise programme	1-hour sessions twice a week	12 weeks	Yoga group (n=13) and exercise group (n=13)	Quality of life, balance, physical function, and pain	NR	Both yoga training and classical osteoporosis exercises had beneficial effects on balance and quality of life. Compared with yoga, the exercise programme demonstrated significant improvements in pain and functional activities	Yoga training seems to be more effective than classical exercises
Sinaki, 2013	Three cases of women with osteopenia	Strenuous yoga flexion exercises	NR	Woman C performed for 10 weeks	N/A	Back pain and vertebral compression fractures	Were in good health and pain-free	Severe back pain and vertebral compression fractures	In older persons, flexibility of the spine achieved with yoga can lead to adverse effects rather than benefits
Cesarec, 2014	Women with osteopenia or osteoporosis	Osteoporosis exercise programme Supervised exercise programme.	30-45 minutes	4 weeks	Before and after design	Quality of life	NR	Significant improvement in all nine dimensions of the quality of life questionnaire (physical functioning, role-physical, role-emotional, social functioning, mental-health, vitality, bodily pain, general health and general health status) compared to the period a year ago.	Programmed physical activity program for osteoporosis is effective and affects the psychological aspects of patient's life

Table 2. *(cont. from previous page).*

Lead author, publication date	Population	Type of physical activity or exercise	Frequency of physical activity or exercise program	Total duration of physical activity or exercise	Intervention groups	Adverse outcome measures assessed	Baseline status prior to study entry	Reported findings	Study conclusions
Hakestad, 2015	Postmenopausal women with osteopenia and a healed forearm fracture	Exercise programme combined with a patient education program called OsteoINFO. Consisted of 2 group exercise sessions and 1 home exercise session per week. The program included exercises for strength, balance, coordination, and core stability, and included the use of weight vests. Also incorporated into the programme were ergonomic exercises, such as rising from a lying to a standing position and lifting heavy weights while maintaining the spine in a neutral position and keeping the weights close to the body. Supervised and unsupervised exercise programme.	Three 60-minute sessions per week.	6 months	Before and after design	Joint pain, muscle soreness, and falls	Past history of fracture, median (min-max): 2 (1-3)	No adverse events reported	A 6-month active rehabilitation program, which included an exercise program with the use of a weight vest in addition to a patient education program is feasible, had high adherence with no adverse events. The results however cannot be generalized to patients with severe established osteoporosis or to those with vertebral or hip fracture
Lu, 2016	Majority of patients with osteoporosis or osteopenia	Yoga regimen consisting of 12 poses Web-based program	12-minute sessions daily	2 years	Before and after design	Compliance and self-reported and radiological measures of injury	109 fractures reported on radiographs prior to study entry	After more than 90,000 hours of Yoga, no self-reported or radiographic fractures or serious injuries related to yoga have been reported by any of the participants.	The 12 yoga poses studied here appear to be a safe and effective means to reverse bone loss in the spine
Oh, 2016	Two cases of women with low bone mineral density	Horseback riding	Once a week and 1 hour every week day respectively	1 and 2 months respectively	N/A	Back pain and vertebral compression fractures	Woman A History of hypercholesterolaemia and total hysterectomy without adnexectomy due to myoma. Woman B History of hyperlipidaemia, osteoporosis, and regular menstruation	Woman A felt upper back pain after her fourth riding lesson. Back pain lasted for 4 months. A radiograph confirmed a vertebral compression fracture. Woman B reported back pain that was aggravated by horseback riding. A radiograph confirmed a vertebral compression fracture.	Horse riding in osteoporosis may cause back pain and vertebral compression fractures

N/A, not applicable; SD, standard deviation.
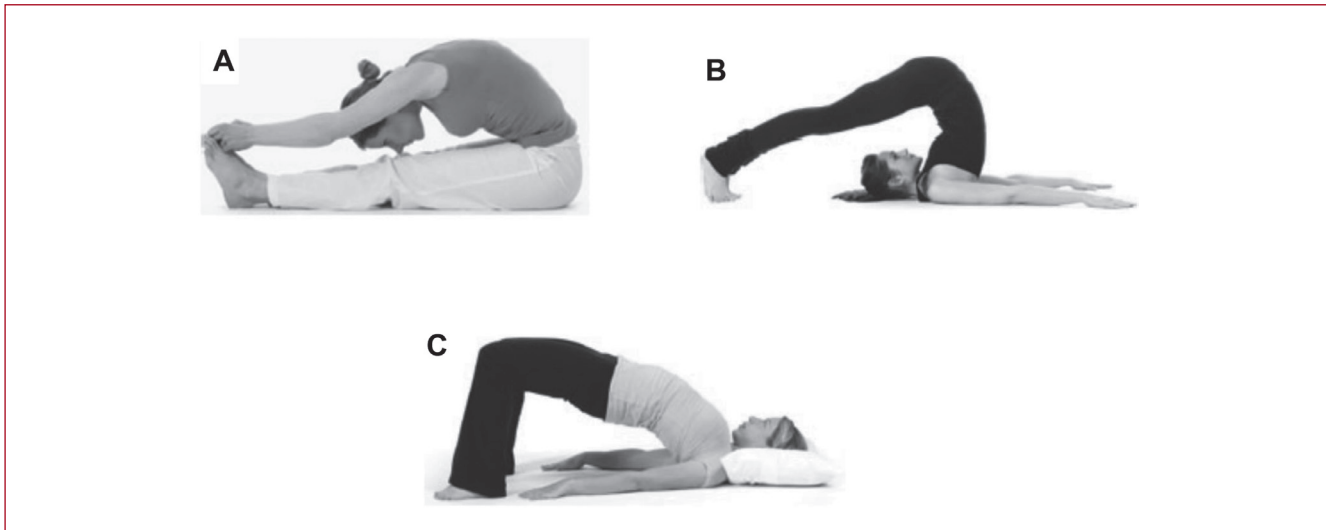
Figure 2. Common yoga poses associated with extreme spinal flexion (adapted from Sinaki MS 2013). (A) Paschimottasana (seated forward bend/fold); (B) Halasana (Plow yoga pose); and (C) Setu Bandha Sarvangasana (Bridge yoga pose).

Studies reporting no, reduced or unchanged adverse events

The majority of studies (ten out of fourteen) either reported no adverse events, reduced incidence/improvement in adverse events, or no significant change in adverse events after physical activity or exercise (Table 2). These beneficial effects were not confined to any specific age group of patients, but the majority of participants in these studies were women. All participants in these studies had low bone mass, defined by a variety of methods including DXA T score <-1.0[23], DXA Z score <-1.0[22], DXA T score <-1.5[26], DXA T score <-2.5[21,30], neutron activation analysis[20] or undefined[24,25,31,32]. Some studies included participants with previous low trauma fractures[20,22,26]. Some studies did not mention use of medications to reduce fracture risk by participants[23,25,31,32]; some reported all participants were on calcium supplementation[20,21] or bisphosphonates[30]; and some reported that a proportion of participants were taking calcium supplements[22,26], oestrogen[20-22], sodium fluoride[20,22] or 'other medications known to affect bone homeostasis'[21]. One study reported no participants were on any medications to reduce fracture risk nor calcium supplements[24]. Many of these studies, with no or reduced rates of adverse events, excluded participants with additional medical problems or illnesses including metabolic bone diseases or those that may be associated with secondary osteoporosis[22-25,30,32], participants with reduced cognition[23,25], smokers[22,24], those who lived in care facilities[23,25], those who used walking aids[25], or those who already participated in regular exercise[23-25]. One study excluded participants with severe osteoporosis as defined by previous hip or vertebral fractures, or a history of more than three low trauma fractures[26].

In a study of daily outdoor walking at moderate intensity for 12 months in postmenopausal women with osteoporosis or osteopenia (exercise group versus controls), none of the participants suffered any fractures during the study period[24]. However, the authors noted in their conclusion that their sample size was too small and study period too short to detect the effect of exercise on the risk of vertebral fracture. Hakestad and colleagues in their before-after design study reported no adverse events (joint pain, muscle soreness, and falls) after 6 months of an exercise programme combined with an education programme[26]. After over 90,000 hours of a yoga regimen, no self-reported or radiographic fractures or serious injuries related to yoga were reported by any of the participants in the study by Lu and colleagues[32]. It is of note that they specifically chose poses that were 'safe'. Walker and colleagues reported a reduction in incidence of fractures after a 5-year follow-up of an exercise programme which consisted of a 20-minute low load, strength training session and 30 minutes of aerobic activities[21]. After 12 weeks of Tai Chi in community-dwelling women with or at risk for osteoporosis, there was no significant change in the incidence of falls[25]. In a study that compared participants in a home exercise programme with controls, there were no differences between the groups in terms of fracture rates, falling episodes, and neuromuscular performance[22]. In a 12-week comparison of a yoga programme with a classical osteoporosis exercise programme, both yoga training and exercises had beneficial effects on balance and quality of life. Compared with yoga, the exercise programme demonstrated significant improvements in pain and functional activities[30].

Studies associated with adverse events

The findings of one study suggested that a number of vertebral compression fractures occurred in patients with

postmenopausal spinal osteoporosis who undertook spinal flexion exercises compared with extension exercises[19]. In this study, participants were 59 women aged 49 to 60 years, with a 'radiographic diagnosis' of spinal osteoporosis. Use of medications to reduce fracture risk was not reported. Women older than 60, with reduced cognition, or with other medical problems such as cancer, metabolic bone diseases or potential causes of secondary osteoporosis were excluded. Those participants who carried out spinal flexion exercises (sitting in a chair, leaning forward with arms hanging down and head bent forward, and stretching the erector spinal muscles by forward flexing the spine such as sit-ups) were more likely to develop new vertebral fractures than those who carried out spinal extension exercises. No other differences, apart from exercise type, were reported between those participants who developed vertebral fractures and those who did not.

A report of three cases of women (aged 87, 61 and 70) with osteopenia measured by DXA (T scores less than -1.0), unknown medication usage, but in otherwise good health and pain-free, reported participation in yoga involving spinal flexion exercises resulted in back pain and vertebral compression fractures[28]. The specific yoga poses were the Paschimottasana pose (seated forward bend/fold or the half-hero stretch), the Halasana pose (Plow yoga pose) and the Setu Bandha Sarvangasana (Bridge yoga pose) (Figure 2).

In a case report of two women (aged 44 and 49), one with a DXA T score -1.9 and one with undefined 'osteoporosis', neither on any medications to reduce fracture risk, horseback riding was associated with new onset back pain and vertebral compression fractures[27]. Both fractures occurred whilst the horse was walking, not jumping over obstacles. In an additional case report, three postmenopausal women (aged 54, 58 and 66) with DXA T scores <-1.3, one of whom had previously taken calcium supplementation and medications to reduce fracture risk, who were all experienced golfers suffered acute pain and vertebral compression fractures during a golfing mid-swing stroke[29]. One further study of an 'exercise programme modified to meet individual requirements' reported an increased proportion of vertebral fractures in the subgroup who showed the least improvement in fitness[20], but in a 5-year follow-up report of the same study, the incidence of fractures was significantly reduced over the course of the study period[21].

Robustness of findings from observational and non-randomised studies

Though the reported conclusions from the included studies generally suggested physical activity and exercise to be beneficial and safe for patients living with osteoporosis and osteopenia (Table 2); the findings should be interpreted with caution given some limitations in the methodological quality of the eligible studies such as the study designs (observational cohorts and case reports), lack of appropriate controls in some of the studies, self-reports of outcomes by study participants, selective reporting of outcomes, and authors of studies being involved in design of interventions. Few studies recruited women over the age of 60 or with co-morbid conditions.

Excluded studies

The list of excluded studies after full-text evaluation is provided in Appendix 3. Reasons for exclusion were irrelevant populations recruited (participants without osteoporosis or osteopenia), outcomes, and study designs. One was a review of case reports and series evaluating the adverse events associated with yoga[33] but had not identified any additional papers to the yoga papers identified by this review.

Results: update of interventional data

Exercise to prevent and treat osteoporosis in post-menopausal women, by Howe et al.[13]

1471 trials were identified, and following screening, full texts were acquired for 76 trials for consideration (see Appendix 4). After scrutiny, 27 additional trials were included. When added to the 35 previous trials, the update contains information from 62 trials involving a total of 6607 participants. Supervision of exercise intervention varied across studies, with one supervised by a physiotherapist[34], 14 by a combination of research staff or exercise class staff[35-48], and 5 mixed independent at home and supervised gym classes[47,49-52]. Overall, 70% of the interventions were supervised. 16 of the additional trials did not report whether the intervention was supervised.

11 trials reported on numbers of fractures occurring as an adverse event. In these 11 studies, there were 31 fractures occurring in 536 intervention group participants (5.8%) and 43 fractures occurring in 449 control group participants (9.6%). Meta-analysis showed a trend for the intervention to reduce fractures (OR 0.60, 95%CI 0.36 to 1.01, P=0.053). Nine studies reported on falls occurring as an adverse event. In the pooled analysis there was no effect of exercise on falls overall (RR 1.04, 95%CI 0.79 to 1.37, P=0.779). 24 studies reported on minor adverse events including joint pain, muscle soreness, headaches, and itchiness. The overall pooled effect was an increase in these minor adverse events reported by the intervention group participants (RR 1.55, 95%CI 1.05 to 2.28, P=0.029). In most cases reported, these minor adverse events did not stop participation in the study. Two trials reported serious adverse events[53,54] with one myocardial infarction and one asthma attack in the intervention groups, and one myocardial infarction and one cardiac dysrhythmia in the control groups.

Exercise for improving outcomes after osteoporotic vertebral fractures, by Giangregorio et al.[14]

568 trials were identified, and following screening, full texts were acquired for 17 trials for consideration (see Appendix 5). After scrutiny, 3 additional trials were

included. When added to the 7 previous trials, the update contains information from 10 trials involving a total of 678 participants. None of the new trials included male participants. The interventions varied across the three additional studies. Two were undertaken twice weekly[50,55] whilst the other was three times per week[56]; low intensity exercise consisting of pelvic, abdominal and spinal control exercise was used by one trial[56], no intensity was specified in the trial that used a structured programme including stretching, strength training and weight-bearing exercises[50], and no intensity was specified in the study that used a circuit training programme involving balance training, agility training and postural exercises[55].

There was no indication that adverse events were systematically monitored in any of the included studies. One study reported no adverse events[55]. One study reported two serious adverse events of breathing difficulties experienced by two participants whilst undertaking functional exercises during activities of daily living[56]. In the study by Evstigneeva et al., four participants in the intervention and two in the control sustained a fracture. Vertebral fractures occurred equally between intervention and control groups with two in each group. There were five non-vertebral fractures in the control and two in the intervention group, a difference which was not significant[50]. There was also one report of worsening knee pain attributable to the intervention[50].

Exercise to prevent falls in older adults by Sherrington et al.[12]

1982 trials were identified, and following screening, full texts were acquired for 68 trials for consideration (see Appendix 6). After scrutiny, 19 additional trials were included. When added to the 88 previous trials, the update contains information from 107 trials involving a total of 23,288 participants. 16 of the additional trials were randomised by individual, three were cluster randomised (one by General Practitioner[57], one by retirement village[58] and one by health centre[59]), and one used a cross-over design[60]. Greater than 50% of participants in the additional trials were female. Four trials recruited on the basis of participants having a clinical diagnosis of Parkinson's Disease[60-63], one with visual impairment[64] and one with a clinical diagnosis of osteoporosis[60]. Either a history of falls or having at least one risk factor for falls such as frailty or balance impairment were a pre-requisite for participants in eight trials. Severe or significant cognitive impairment was used as an exclusion criterion in >50% of the trials.

55 trials (51.4%), including 8 of the additional trials, did not report on adverse events. 26 trials (24.2%) reported an occurrence of zero adverse events, of which seven were reported as no serious adverse events only[64-70]. Data presentation for adverse events was highly heterogeneous between trials, with some reporting only those events deemed attributable to the intervention. Out of 11 participants randomised to the intervention group in Wesson

et al.[71], four reported mild complaints of pain, dizziness and stiffness. Complaints were resolved by exercise modification. Sherrington et al.[72] reported 12 adverse events attributable to the exercise intervention including muscle and joint pain, and exacerbations of pre-existing symptoms. Other trials reported all adverse events that occurred in its participants regardless of study arm. For example, Dean et al.[73] reported three deaths, all control group participants, in addition to one participant suffering from exacerbation of incontinence as a result of the exercise intervention. Sparrow et al.[60] in women with osteoporosis, reported 7 adverse events, of which only two (one knee and one quadriceps pain) were deemed attributable to the intervention. Only one trial reported two adverse serious events attributable to the intervention: Clemson et al.[74] reported a groin strain followed by surgery for inguinal hernia in the structured exercise group, and one pelvic stress fracture in the Lifestyle Integrated Functional Exercise group (participants with known osteoporosis was not an exclusion criteria for this trial). Eight trials of community-dwelling participants reported on the number of adverse events for intervention and control participants. The pooled effect of adverse events associated with the intervention in this group was 1.08 (95%CI 1.04 to 1.13). In a study evaluating the effect of brisk walking on post-menopausal women who had previously sustained a distal forearm fracture, the intervention group had significantly more falls in the first year of follow-up compared to the control group (42 and 26 falls per 100 person years respectively)[75].

The incidence of the commonly reported adverse events was calculated as person-years. Trials in this review reported falls to be the adverse event with the highest incidence (156/1000 person-years). The next most frequently reported adverse events were musculoskeletal complaints such as muscle strain and soreness and joint/unspecified pain (132/10000 person-years). Fractures were reported with the lowest incidence (21/1000 person-years).

Discussion

Key findings

We have systematically reviewed the evidence on the adverse effects of physical activity and/or exercise on adults with osteoporosis or osteopenia. In a comprehensive search we identified 71 studies (14 observational studies comprising of 11 observational cohorts and three case reports; and 57 randomised controlled trials in an update of three previous systematic reviews of interventional evidence) which met our inclusion criteria. The results were consistent for the great majority of observational studies – no reported incidences in adverse events, reduced incidence or improvement in adverse events, or no significant change in adverse events after physical activity or exercise. However, most included supervised initial instruction to check technique. Most of these studies and reports did not include men or older women, and excluded those with multiple co-morbidities or secondary osteoporosis. The updated systematic reviews of

interventional data highlighted that none of the trials were powered to look at adverse events including fractures, and these were poorly reported. However, although participants in the exercise groups reported more adverse effects than those in the control groups, these were mainly minor adverse events and did not stop participation. Severe or serious adverse events were rarely reported. Overall, our conclusion is that most physical activities and structured exercise programmes are safe for postmenopausal women with osteoporosis or low bone mass. Care, however, should be taken by those naïve to activities which may increase risk (horse riding, golf and yoga or sit-ups) as technique is obviously important to adverse outcomes.

Implications of our findings: overall conclusion is that physical activity or exercise is safe for patients with osteoporosis or low bone mass

The generally consistent findings reported by the included studies suggest that physical activity or exercise is safe for patients with osteoporosis or low bone mass. No clear difference in serious adverse events was identified between supervised or unsupervised exercise programmes. Furthermore, the updated meta-analysis of interventional studies has provided the first evidence to suggest that exercise interventions for bone health can reduce fractures. The increase in minor adverse events identified in the interventional studies is what would normally be expected with physical exertion such as muscle aches. Given the variation in the frequency, intensity, and duration of the exercise programmes reported by eligible studies, no conclusions could be made as to whether these factors affected the rate of occurrence of adverse events. However, the reports do suggest that the prescribed exercise programmes were tailored or modified to meet the individual requirements of the patients. The current findings are very relevant as they provide several implications for clinical practice. Health professionals have often questioned the safety of recommending physical activity or exercise programmes in addition to pharmacological interventions to patients with osteoporosis. As a result, healthcare professionals can be extremely cautious when recommending physical activity or exercise for these patients. Patients with osteoporosis also tend to restrict physical activity due to the fear of falling or sustaining fractures[76] – so-called 'kinesiophobia'[77]. However, there is evidence that being involved in exercise programmes can actually reduce both falls and the fear of falling[12,78]. Considering the growing evidence that sedentary behaviour, and in particular prolonged periods of sitting, can reduce bone mass and physical function, hence leading to more falls and frailty, there is a need to reverse this behaviour[79-81]. Taking the overall evidence together, being physically more active and perhaps joining exercise programmes should be recommended for patients with osteoporosis and osteopenia.

Types of exercise or physical activity that may have an increased risk of adverse events in patients with osteoporosis or low bone mass

Our findings from the observational data suggest that repetitive spinal flexion exercises, horseback riding, and golfing may be associated with a greater risk of adverse events such as back pain and vertebral compression fractures, although the evidence on horseback riding and golfing is based on one case series each and must be interpreted with caution. The evidence suggesting that spinal flexion may be associated with vertebral fractures is based on two papers only[19,28]. However, it is mechanically plausible that forward flexion increases the load on the front of the vertebral bodies, and is likely to increase the risk of vertebral fractures[82]. It therefore seems reasonable to recommend that people with osteoporosis avoid specific and repetitive spinal forward flexion exercises, and instead focus on spinal extension. However, it needs to be emphasized that evidence that forward flexion exercise interventions cause vertebral fractures are limited and caution should be used in giving advice to patients about appropriate movements based on their low BMD measurements alone. Pragmatically it makes sense for older people who may be at risk of fractures to avoid brisk walking as there appears to be an increased risk of falls with brisk walking as opposed to walking at a normal speed[12], and also repetitive or loaded forward flexion. However, there is no evidence that single forward flexion movements in daily activities or 'roll down' Pilates movements cause vertebral fractures – a common misconception [personal communication from SL based on the National Osteoporosis Society charity's helpline statistics on common concerns expressed by patients]. There should be a focus on how to lift weight or pick up things from the floor safely so that everyday activities that involve spinal flexion are performed with good technique[15]. In terms of specific yoga poses that appear to increase risk, there are modified versions of all yoga poses that experienced teachers can recommend, rather than avoiding yoga completely. In addition, it is important to highlight that proper instruction on correct spinal movements during general daily life is relevant to everyone, not just those with low bone density.

Equestrian sport is a popular but potentially hazardous recreational activity, with approximately one in five riders suffering a serious injury during their riding career[83]. This makes it difficult to interpret the report of two cases of vertebral fractures occurring in women with low bone density during horseback riding[27]. The authors suggest that the potential reasons that the vertebral fractures occurred were the low bone density, but also the fact that these were less skilled riders who were not absorbing the movements of the horse, instead of sitting stiff and tense. It may, therefore, be sensible for healthcare professionals to discuss the potential increased risk of vertebral fractures in amateur horseback riders with low bone density. However, it is difficult to draw a strong conclusion to suggest avoiding this activity,

particularly when there may be many additional associated quality of life benefits including having a keen leisure interest, a positive owner-animal relationship and social interactions. Perhaps those who are experienced horse riders may not have the same potential adverse events. Similarly, golfing is a popular sport amongst older people as it is challenging without undue exertion, is socially fulfilling and is associated with physical health benefits and improved wellness[84]. However, the incidence of golfing injury is moderate, with back injuries the most frequent[84], again making it difficult to draw strong conclusions from the limited evidence of vertebral fractures occurring during a golfing mid-swing in three older women with osteoporosis[29]. The authors of this paper suggest that a rigid back support for golfers with osteoporosis may protect against fractures, but no evidence was provided that such an orthosis is beneficial. Nonetheless, it would be important for healthcare professionals to discuss the potential increased risk of vertebral fractures during golf swings, without making firm conclusions about avoiding this activity. Instead, if golf is important to someone, the risk/benefits of continuing should be discussed.

Gaps in the literature

Our review has also identified gaps in the existing evidence which include: (i) uncertainty around which age groups are more at risk of adverse events; (ii) whether supervised or unsupervised exercise programmes are associated with a higher risk of adverse events; (iii) uncertainty on the relationship between the severity of osteoporosis and occurrence of adverse events and no evidence on the association between people with high fracture risk as assessed by tools such as FRAX and adverse events; (iv) lack of evidence for men with osteoporosis; (v) lack of evidence for the very elderly; (vi) lack of studies including participants with multiple co-morbidities or secondary osteoporosis; and (vii) lack of clear reporting of adverse events in interventional exercise and physical activity studies. In light of these further robust research is needed, particularly as it is unclear whether the many studies identified in this review that did not report any adverse events were doing so because none occurred, or because the data was not recorded.

Strengths and limitations

This review is the first to our knowledge to systematically examine the adverse effects of physical activity and/or exercise on adults with osteoporosis or osteopenia in non-randomised studies. We have also updated the evidence on previous findings from interventional studies. We have attempted to ascertain the baseline characteristics of people who experience adverse events after physical activity and/or exercise, explored the various types of physical activity or exercise being undertaken by these patient populations, and identified gaps in the evidence. We employed a detailed literature search which spanned several databases. The review of observational and non-randomised studies was limited by the potential for biases in the study designs employed. However, these study design criteria were used because recent systematic reviews of exercise and physical activity interventions on bone health report adverse events already. The generalizability of the findings is also limited by: (i) the greater majority of studies focusing on only postmenopausal women; (ii) the exclusion criteria used by the majority of eligible studies and therefore populations recruited did not include patients with additional medical problems or illnesses including metabolic bone diseases or those that may be associated with secondary osteoporosis, or those who lived in care facilities; and (iii) physical activity or exercises covered were mainly group-based exercise programmes containing common physical activities used within the general population and not high impact activities such as tennis, running or aerobics. Finally, we did not carry out a de-novo systematic review and evidence synthesis of all interventional studies for adverse events, instead of updated three previously performed systematic reviews that focussed on exercise and physical activity interventions in people who are likely to have low bone mass or are at high risk of falls. While this is an unorthodox approach, it does allow a wide-ranging summary of the available literature, both randomised and non-randomised, within a single paper.

Conclusions

On the basis of available evidence, people with osteoporosis or osteopenia can be reassured that they can safely participate in common exercise programmes whether at home or in supervised facilities and many unstructured physical activities. However, as expected with participation in physical activity and exercise, minor adverse events such as muscle ache may occur. Specific repetitive forced spinal forward flexion exercises should be undertaken with care as they may be associated with an increased risk of new vertebral fractures. Some types of activities such as brisk walking, horseback riding and golfing need to be discussed on an individual basis, as they may not be appropriate. These findings, however, cannot be generalized to patients with additional medical problems or illnesses, or those who live in care facilities. Further research focussing on efficacy of exercise or physical activity on bone health should focus on reporting adverse events in different age groups or DXA scores, should include men and should consider those that are normally excluded from such studies (see above).

Statement on Exercise and Physical Activity for Osteoporosis 2017-2018. SL is an Osteoporosis Nurse Consultant at the National Osteoporosis Society and did not take part in the analysis but contributed to the interpretation and discussion.

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Supplementary Material

Appendix 1

PRISMA checklist.

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	6
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	6
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Appendix 2
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	6-7
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	6-7
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	6-7
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Not applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Not applicable
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Not applicable
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Not applicable
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	8 and Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	8 and Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	8-13, Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Not applicable
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Not applicable
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	14
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	18
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	19

Appendix 2

Literature search strategy.

Relevant studies, published before June 27, 2017 (date last searched), were identified through electronic searches not limited to the English language using MEDLINE, EMBASE, CINAHL, and Web of Science. Electronic searches were supplemented by scanning reference lists of articles identified for all relevant studies (including review articles) and by hand searching of relevant journals. The computer-based searches combined search terms related to physical activity or exercise, adverse events, and osteoporosis.

1	exp Osteoporosis/ (51404)	36	exp Lifting/ (2367)
2	osteoporo$.mp. (80014)	37	Exertion.mp. (65871)
3	fragility fracture.mp. (1070)	38	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 (684603)
4	osteopenia.mp. (8354)		
5	bone loss.mp. (30385)		
6	bone mass.mp. (16652)		
7	exp Bone Density/ (47932)	39	Adverse events.mp. (107914)
8	bone mineral density.mp. (34542)	40	Side effects.mp. (221346)
9	Demineralised bone.mp. (103)	41	exp Fractures, Bone/ (167159)
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (131986)	42	exp "Wounds and Injuries"/ (827548)
11	exp Exercise/ (158559)	43	Injuries.mp. (496425)
12	Physical activity.mp. (82304)	44	Broken bones.mp. (182)
13	exp Exercise Therapy/ (41437)	45	exp Accidental Falls/ (19889)
14	exp Physical Exertion/ (56792)	46	Falls.mp. (47112)
15	exp Physical Fitness/ (25995)	47	exp Pain/ (356057)
16	exp Physical Endurance/ (30348)	48	Physical function.mp. (9795)
17	exp Sports/ (161452)	49	Muscle function.mp. (9359)
18	exp Pliability/ (4238)	50	Balance.mp. (212767)
19	exp Physical Therapy Modalities/ (133497)	51	Mobility.mp. (139058)
20	exp Resistance Training/ (5979)	52	39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 (1886764)
21	exp Weight Lifting/ (4456)		
22	exp Weight Lifting/ (4456)	53	exp Epidemiologic Studies/ (2101541)
23	exp Rehabilitation/ (270150)	54	exp Case-Control Studies/ (883169)
24	Physiotherapy.mp. (15298)	55	exp Cohort Studies/ (1701977)
25	exp Vibration/ (23192)	56	cohort analysis.mp. (5723)
26	Vibration therapy.mp. (132)	57	exp Follow-Up Studies/ (590703)
27	exp Running/ (17825)	58	exp Prospective Studies/ (462547)
28	Cycling.mp. (47684)	59	exp Longitudinal Studies/ (110993)
29	exp Swimming/ (22288)	60	exp Retrospective Studies/ (658490)
30	exp Skiing/ (3253)	61	exp Cross-Sectional Studies/ (249728)
31	exp Yoga/ (2157)	62	Case series.mp. (54067)
32	pilates.mp. (310)	63	exp Case Reports/ (1890524)
33	Tai chi.mp. (1281)	64	53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 (3922083)
34	exp Hydrotherapy/ (19190)		
35	Bending.mp. (26784)	65	10 and 38 and 52 and 64 (1109)
		66	limit 65 to (humans and "middle aged (45 plus years)") (854)

Each part was specifically translated for searching the other databases (EMBASE, CINAHL, and Web of Science databases)

Appendix 3

Reference list of excluded studies.

1. Cauley JA, Harrison SL, Cawthon PM, Ensrud KE, Danielson ME, Orwoll E, Mackey DC. Objective measures of physical activity, fractures and falls: the osteoporotic fractures in men study. J Am Geriatr Soc 2013;61:1080-1088.
2. Cramer H, Krucoff C, Dobos G. Adverse events associated with yoga: a systematic review of published case reports and case series. PloS one 2013;8:e75515.
3. Dohrn IM, Hagstromer M, Hellenius ML, Stahle A. Gait Speed, Quality of Life, and Sedentary Time are Associated with Steps per Day in Community-Dwelling Older Adults with Osteoporosis. J Aging Phys Act 2016;24:22-31.
4. Gerdhem P, Ringsberg KA, Akesson K, Obrant KJ. Influence of muscle strength, physical activity and weight on bone mass in a population-based sample of 1004 elderly women. Osteoporos Int 2003;14:768-772.
5. Gregg EW, Cauley JA, Seeley DG, Ensrud KE, Bauer DC. Physical activity and osteoporotic fracture risk in older women. Study of Osteoporotic Fractures Research Group. Ann Intern Med 1998;129:81-88.
6. Huovinen V, Ivaska KK, Kiviranta R, et al. Bone mineral density is increased after a 16-week resistance training intervention in elderly women with decreased muscle strength. Eur J Endocrinol 2016;175:571-582
7. Kronhed AC, Moller M. Effects of physical exercise on bone mass, balance skill and aerobic capacity in women and men with low bone mineral density, after one year of training--a prospective study. Scand J Med Sci Sports 1998;8:290-298.
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14. Sze PC, Cheung WH, Lam PS, Lo HS, Leung KS, Chan T. The efficacy of a multidisciplinary falls prevention clinic with an extended step-down community program. Arch Phys Med Rehabil 2008;89:1329-1334.
15. Tsutsumimoto K, Doi T, Shimada H, Makizako H, Yoshida D, Uemura K, Anan Y, Park H, Suzuki T. Self-reported exhaustion associated with physical activity among older adults. Geriatr Gerontol Int 2016; 16:625-630.
16. Vaillant J, Vuillerme N, Martigne P, Caillat-Miousse JL, Parisot J, Nougier V, Juvin R. Balance, aging, and osteoporosis: effects of cognitive exercises combined with physiotherapy. Joint Bone Spine 2006;73:414-418.
17. Villareal DT, Binder EF, Yarasheski KE, Williams DB, Brown M, Sinacore DR, Kohrt WM. Effects of exercise training added to ongoing hormone replacement therapy on bone mineral density in frail elderly women. J Am Geriatr Soc 2003;51:985-990.
18. Grahn Kronhed A-C, Hallberg I, Ödkvist L, Möller M. Effect of training on health-related quality of life, pain and falls in osteoporotic women. Advances in Physiotherapy. 2009;11(3):154-65.

Appendix 4

Flow diagram of study selection process for updated Howe review.

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        ┌─────────────────────────────┐
        │   1471 records identified   │
        │  through database searching │
        └─────────────┬───────────────┘
                      │
                      ▼
        ┌─────────────────────────────┐
        │   951 records after duplicates │
        │           removed           │
        └─────────────┬───────────────┘
                      │
  ┌──────────────────┐│
  │ 1 additional record identified │
  │   through other sources        │──►
  └──────────────────┘│
                      ▼
        ┌─────────────────────────────┐      ┌─────────────────────────────┐
        │    952 records screened     │─────►│  876 records excluded – not │
        │                             │      │           relevant          │
        └─────────────┬───────────────┘      └─────────────────────────────┘
                      │
 ┌──────────────────────────┐
 │ 41 excluded because:      │
 │ Incorrect control group (3)│
 │ Conference poster for     │
 │ included study (2)        │◄─┐
 │ Incorrect participants (9)│  │   ┌─────────────────────────────┐
 │ Inappropriate intervention│  └───│ 76 full-text articles assessed │
 │ (2)                       │      │        for eligibility       │
 │ No outcome of interest (9)│      └─────────────┬───────────────┘
 │ Incorrect study type (11) │                    │
 │ Duplicate data (4)        │                    ▼
 │ Non-English (1)           │      ┌─────────────────────────────┐      ┌─────────────────────────────┐
 └──────────────────────────┘      │  35 studies included in     │─────►│  8 studies excluded – not   │
                                    │    qualitative synthesis    │      │          relevant           │
                                    └─────────────┬───────────────┘      └─────────────────────────────┘
                                                  │
                                                  ▼
                                    ┌─────────────────────────────┐
                                    │ 27 additional studies included │
                                    │  in quantitative synthesis   │
                                    └─────────────────────────────┘
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Appendix 5

Flow diagram of study selection process for updated Giangregorio review.

```
                    ┌─────────────────────────────┐
                    │   678 records identified    │
                    │  through database searching │
                    └──────────────┬──────────────┘
                                   │
                                   ▼
                    ┌─────────────────────────────┐
                    │  568 records after duplicates│
                    │           removed            │
                    └──────────────┬──────────────┘
┌───────────────────────────┐     │
│ 0 additional record       │     │
│ identified through other  │─────┤
│ sources                   │     │
└───────────────────────────┘     ▼
                    ┌─────────────────────┐      ┌─────────────────────────┐
                    │ 568 records screened │─────▶│ 551 records excluded –   │
                    └──────────┬──────────┘      │     not relevant         │
                               │                  └─────────────────────────┘
                               ▼
┌──────────────────────────────┐   ┌─────────────────────────┐
│ 14 excluded because:          │   │ 17 full-text articles    │
│ Incorrect study type (2)      │◀──│ assessed for eligibility │
│ Duplicate data (3)            │   └───────────┬─────────────┘
│ No vertebral fracture at      │               │
│ baseline (3)                  │               ▼
│ Conference abstract with not  │   ┌─────────────────────────┐
│ enough information (7)        │   │ 3 studies included in    │
└──────────────────────────────┘   │ qualitative synthesis    │
                                    └───────────┬─────────────┘
                                                │
                                                ▼
                                    ┌─────────────────────────┐
                                    │ 0 additional studies     │
                                    │ included in quantitative │
                                    │ synthesis (meta-analysis)│
                                    └─────────────────────────┘
```

Appendix 6

Flow diagram of study selection process for updated Sherrington review.

```
                    ┌──────────────────────────┐
                    │ 4264 records identified   │
                    │ through database searching│
                    └──────────────────────────┘
                                 │
┌──────────────────────┐        │
│ 2282 duplicates      │◄───────┤
│ removed              │        │
└──────────────────────┘        │
                    ┌──────────────────────────┐
                    │ 1982 trials screened by  │
                    │ title                    │
                    └──────────────────────────┘
                                 │              ┌──────────────────────────┐
                                 ├─────────────►│ 1407 records excluded –   │
                                 │              │ not relevant              │
                                 │              └──────────────────────────┘
                    ┌──────────────────────────┐
                    │ 575 screened by abstract │
                    └──────────────────────────┘
                                 │              ┌──────────────────────────┐
                                 ├─────────────►│ 507 studies excluded –    │
┌──────────────────────────┐    │              │ not relevant              │
│ 49 excluded because:      │    │              └──────────────────────────┘
│ No falls (17)             │    │
│ Conference abstracts/paper│ ┌──────────────────────────┐
│ not available (7)         │ │ 68 full-text articles     │
│ Control (6)               │ │ assessed for eligibility  │
│ Mean age <65 (6)          │ └──────────────────────────┘
│ Intervention (6)          │◄──────┤
│ In previous Sherrington   │       │
│ review (5)                │ ┌──────────────────────────┐
│ Systematic reviews (but   │ │ 19 additional studies     │
│ checked for relevant      │ │ included in quantitative  │
│ articles) (2)             │ │ synthesis                 │
└──────────────────────────┘ └──────────────────────────┘
```