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REVIEW

Patient education in osteoporosis prevention: a systematic review focusing on methodological quality of randomised controlled trials

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Abstract
Summary This review summarizes evidence regarding the effects of patient education in osteoporosis prevention and treatment. The included studies reveal mixed results on a variety of endpoints. Methodological improvem ent of future RCTs (e.g. with regard to randomization and duration of follow-up) might yield more conclusive evidence on the effects of patient education in osteoporosis
Introduction This review aims to evaluate the effects of patient education on osteoporosis prevention and treatment results.
Methods Multiple databases including PubMed and Embase were searched until February 2016. Randomised controlled trials (RCTs) were eligible if they included adults diagnosed with or at risk of osteoporosis and assessed patient education interventions (group- or individual-based). Outcomes regarding osteoporosis management including initiation of and adherence to pharmacological therapy, physical activity, calcium and vitamin D intake, changes in smoking behaviour, fractures, quality of life (QoL) and osteoporosis knowledge were evaluated. The Cochrane collaboration's tool for assessing the risk of bias was used to assess the internal validity of included trials.
Results Fifteen articles (13 different studies) published between 2001 and 2013 were included (group-based education = 7, individual-based education = 5, both = 1). The general risk of bias was considered as moderate to high. The effects on 'bone mineral density (BMD) testing and/or pharmacological therapy' (composite endpoint), 'calcium intake' and 'vitamin D intake' as well as 'osteoporosis knowledge' were statistically significant in favour of the intervention in ≥50% of the studies analysing these outcomes. Differences between the intervention and the control group regarding 'pharmacological therapy', 'medication adherence', 'physical activity', 'fractures' and 'QoL' were found to be statistically significant in <50% of the trials.
Conclusions This review indicates that it is still unclear whether patient education is beneficial and whether it has a significant and clinically relevant impact on osteoporosis management results. Educational programmes for osteoporosis require further investigation within the context of well-conducted RCTs.

Keywords Intervention · Osteoporosis · Patient education · Prevention · Systematic review · Treatment

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Introduction

Osteoporosis is the most common bone disease and represents a major public health problem. [1, 2] It affects about 20% of women and 7% of men aged over 50 years, with half of them suffering an osteoporotic fracture (particularly hip, wrist and

vertebral fractures) [3–7]. In 2000, nine million incident osteoporotic fractures worldwide were estimated [8].

Osteoporotic fractures result in physical and psychosocial consequences for the patient and place a major economic burden on healthcare systems [2, 3, 5, 8–12]. As a consequence of demographic changes and the resulting ageing population, the prevalence and incidence of osteoporosis and its related fractures will increase dramatically in the future [3, 10, 13].

A major problem regarding osteoporosis management is the poor adherence of patients to medical therapy and other treatment recommendations which can result from a lack of patient information [14–17]. Patient education programmes aim to improve osteoporosis knowledge among patients, their adherence, health beliefs, motivation and behaviour [16, 18, 19]. There is moderate to strong evidence that patient education is effective in other chronic diseases [20–23]. Also, several systematic reviews indicate that educational interventions may improve osteoporosis knowledge, adherence and health-directed behaviour (including calcium and vitamin D intake and physical activity) [24–31]. However, these reviews included studies with diverse patient groups, patient education was not always assessed as a single intervention and some of the reviews included both randomised controlled trials (RCTs) and observational studies.

The objective of this systematic review is to assess the effects of patient education on osteoporosis prevention and treatment results for people diagnosed with or at high risk of osteoporosis. We hypothesise that patient education will improve osteoporosis prevention and treatment results, i.e. increase the initiation of and improve the adherence to medical therapy (e.g. bisphosphonates), vitamin D and calcium intake as well as increase physical activity and thereby reduce the fracture rate and improve quality of life (QoL). In contrast to previous reviews, this review focusses on patient education only[1] assesses multiple endpoints relevant for osteoporosis management and, additionally, aims to provide a more detailed evaluation of the methodology and internal validity of included trials.

Methods

Two reviewers independently conducted the literature search, the risk of bias assessment and data extraction. Discrepancies were solved by discussion until consensus was reached.

Literature search

A literature search was carried out in various databases including PubMed, CINAHL, Embase, Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials) and Education Resources Information Center (ERIC) to identify relevant studies. Search terms included osteoporosis, osteoporotic, education, educational and educate as well as terms describing the study design such as random, controlled and clinical. The primary search strategy for PubMed, using a combination of MeSH and free text terms, was as follows: (((((osteoporosis[MeSH Terms]) OR osteoporosis[Title/Abstract]) OR osteoporotic[Title/Abstract])) AND (((education[MeSH Terms]) OR education[Title/Abstract]) OR educat*[Title/Abstract])) AND ((((random*[Title/Abstract]) OR "random allocation"[MeSH Terms]) OR "randomized controlled trial"[Publication Type]) OR "controlled clinical trial"[Publication Type]). To achieve a high sensitivity, alternative search strategies have been applied, which consisted of less specific and alternative search terms such as patient information, self-management, fragility fracture, low bone mass/density and bone loss. Subsequently, Embase, the Cochrane Library, ERIC and reference lists of included studies were searched for further relevant literature.

Inclusion and exclusion criteria

Studies had to fulfil the following inclusion criteria to be classified as relevant:

Patients

- Studies with a mixed or Caucasian population of (i) postmenopausal women, (ii) men and women aged 50 or above or (iii) men and women with confirmed osteoporosis or a history of fragility fractures.

Intervention

- Educational interventions addressing osteoporosis mainly targeted at patients (i.e. interventions primarily targeted at healthcare professionals as well as studies with non-educational measures as the main element of the intervention were excluded)
- Educational interventions including a personal part, i.e. a face-to-face delivery to patients, either individual- or group-based (interventions that solely consist of written or audio-visual material, patient and/or physician reminders and notifications, case manager or self-referral interventions were not considered)

Comparison

- No intervention or usual care (i.e. written materials such as information sheets or brochures about osteoporosis)

[1] I.e. this review does not combine and compare studies with different interventions to improve the detection and treatment of osteoporosis. To concentrate on the effect of patient education, it was limited to this intervention.

Outcomes

- At least one of the following outcomes regarding osteoporosis diagnosis and management: initiation of and adherence to pharmacological therapy, physical activity, calcium and vitamin D intake, changes in smoking behaviour, fractures, QoL and osteoporosis knowledge

Study design

- Randomised controlled trials (including individual and cluster-randomised trials)
- Studies written in English, French, Italian, Spanish and German with no restrictions on publication date

Methodological assessment

To assess the internal validity and potential limitations of the included trials, the Cochrane Collaboration's tool for assessing the risk of bias has been applied [32]. Where possible, study protocols and information from trial registries[2] were obtained, especially to assess the risk of reporting bias. Otherwise the judgement was based on a comparison of prespecified outcomes in the methods section of the publication with those reported in the results section. The risk of bias assessment was done in accordance with the recommendations of the Cochrane handbook. [32]

The domain "blinding of outcome assessment" was assessed separately for two outcome groups. The first group included subjective outcomes such as QoL as well as behavioural outcomes such as exercise behaviour, calcium and vitamin D intake, medication adherence, etc. The second group covered objective outcomes such as bone mineral density (BMD) test, initiation/prescription of drug therapy, fractures and osteoporosis knowledge.

Data extraction and presentation of study results

The following information and data were extracted from each included study: study design, country, publication year, recruitment process, inclusion criteria, sample size, patients' characteristics (e.g. age, gender), drop-out rate, length of follow-up, characteristics of the intervention (incl. delivery mode, scope and length, educator, educational material, non-educational components, follow-up interventions), comparison and outcome data. The presented outcome data are based on intergroup differences between the intervention and the control group (CG). Intragroup changes were not considered. The outcome data presented were based on the results at the end of the follow-up. That is, in trials with multiple time points of measurement, only the findings at the latest time point were considered[3] Where outcome data was presented as percentages, the absolute differences and the 95% confidence interval (CI) were calculated if applicable.

All outcome results were summarised in the following outcome categories: osteoporosis management, lifestyle modifications, fractures, knowledge and QoL.

Statistical evaluations and meta-analyses were not feasible in this review due to the wide variety of applied endpoints. Even in cases where similar parameters have been assessed, varying outcome definitions, evaluation tools and time frames as well as different approaches of reporting data made statistical summaries difficult.

Results

Literature search

The literature search was carried out on the 29th of October 2016. Figure 1 shows the literature search and study selection process. The primary search strategy on PubMed identified 310 records, of which 30 were included after screening titles and abstracts. Overall, 35 publications were included for full-text screening after searching all predefined databases. Out of these, 20 were excluded and 15 fulfilled all inclusion criteria after full-text review. A list of excluded studies including the primary reason of exclusion is provided in appendix A. No additional articles were identified by screening the reference lists of included studies. In total, 15 articles (of 13 different trials) were included in this review.

The 15 included articles were published between 2001 and 2013 and the majority of trials originated from the USA (n = 5) [34–38]. The other studies were conducted in Canada [33, 39, 40], Turkey [41, 42], Australia [43], Spain [44], Denmark [45, 46] and Finland [47]. For trials published twice, for this review, the analyses will be based mostly on Nielsen et al. (2010) [46] and Yuksel et al. (2010) [39] as they represent the main reports of the two trials.

Study characteristics

Twelve of the included RCTs used individual randomisation and one (Guilera et al. [44]) applied cluster randomisation of primary care practises.

[2] Including the following trial registries: ClinicalTrials.gov (www.clinicaltrials.gov), International Standard Randomised Controlled Trial Number (ISRCTN) (www.isrctn.com) and International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/)

[3] Ciaschini et al.[33] constitutes an exception in this case. Here the main interest lies on the outcome data after six months, as they represent the results of the comparison of intervention and usual care. The 12-month evaluation was done to examine whether the intervention effect can be replicated in the control group.

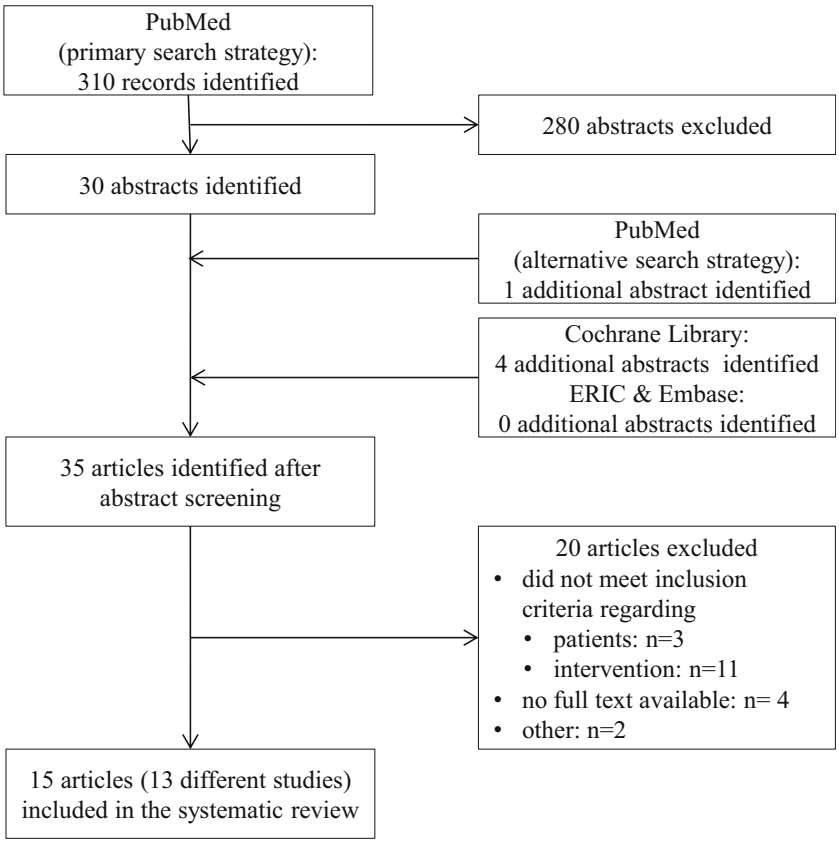

Fig. 1 Flow chart of the literature search and study selection process

A variety of recruitment processes was applied in the included trials. Participants were recruited from outpatient practises (n = 4) [38, 41, 44, 46], through public campaigns such as distributing flyers in the community or newspaper articles (n = 3) [34, 36, 43], from electronic databases (n = 2) [37, 47], hospitals (n = 1) [35] and pharmacies (n = 1) [39]. The majority of studies (n = 9) [33, 36, 38, 41, 43, 46, 47] were conducted in a single site, and three trials [39, 42, 44] were carried out in multiple sites.

The inclusion criteria varied across studies. About half of the trials included both men and women (n = 7) [33–36, 39, 43, 46], while the remaining studies included women only. While most studies did not specify whether their participants had osteoporosis or were at increased risk of osteoporosis/osteoporotic fractures, four studies only included patients diagnosed with osteoporosis [41, 42, 44, 46], and one trial solely focused on patients at high risk for osteoporosis and osteoporotic fractures [39].

Study characteristics regarding the sample size, patients' characteristics, the intervention and comparison as well as the follow-up period are shown in Table 1.

Methodological assessment

Eight trials [33–35, 38, 39, 41–43] used adequate methods for allocation sequence generation, and three [38, 39, 42] out of these also applied adequate methods of allocation concealment. The other five [33–35, 41, 43] did not provide sufficient information on allocation concealment and therefore the risk of bias remains unclear. The most commonly used method for sequence generation was computer-generated random number scheme, and the methods used for allocation concealment were either opaque, sealed envelopes or central randomisation. Three trials [36, 44, 46] did not report sufficient details on their randomisation system, and the risk of bias was unclear regarding both the sequence generation and allocation concealment process. In the remaining two trials [37, 47], the risk of bias was found to be high for these two aspects.

Because blinding of patient education is impossible, there was a high risk of performance bias and detection bias (for subjective and behavioural outcomes)[4] Among the 11 trials which measured objective outcomes, the risk of detection bias

[4] Apart from Gardner et al. [35], who did not assess any subjective or behavioural outcomes.

Table 1 Study characteristics of included trials

Study, follow-up period	Sample size	Patients' characteristics	Intervention Personal component: delivery mode, scope and lengths, educator	Other educational material; follow-up interventions	Other (non-educational) components of intervention	Comparison
Alp et al. [41], 6 months	Total 50 IG 25 CG 25	Mean age 64 ± 8 (IG), 67 ± 11 (CG) sex: all female - History of fracture 30% - Mean T-score (lumbar) −3.8 - Mean T-score (femur) −3.0	Group (size not described); 5 weekly sessions of 50 min; no information given	Exercise video; none	No other components	Usual care
Ciaschini et al. [33], 6 (and12) months[b]	Total 201 IG 101 CG 100	Mean age 72 ± 9 (IG), 71 ± 8 (CG) sex: 94% female - T-score ≤−2.5: 56% - T-score −1.0 to 2.5: 35%	Individual; 1 session (length not described); research nurse	Educational material on calcium, vitamin D and risk factors; none	BMD testing + patient-specific recommendations for osteoporosis treatment were sent to PCP	Usual care*
Francis et al. [43], 6 weeks	Total 198 IG 103 CG 95	Mean age 63 (across both groups) Sex 92% female	Group (size not described); 4 weekly sessions of 2–2.5 h; two trained leaders (health professionals or people with a personal/professional interest in self-management of osteoporosis)	Course manual; none	No other components	Usual care*
Gaines et al. [34], 2 years	Total 376 IG 193 CG 183	Mean age 81 ± 5 (across both groups) Sex: 84% female Ethnicity 99% Caucasian - History of fracture 47% - Osteoporosis diagnosis 35% - Osteoporosis drug use 34%	Group (n = up to 20); 1 × 1 h; no information given	Two osteoporosis brochures + fact sheet describing dietary sources of calcium; ½ hour refresher course after 1 year	Private appointment at baseline and after 1 year incl. QUS screening + screening results were sent to PCP	Usual care
Gardner et al. [35], 6 months	Total 80 IG 40 CG 40	Mean age 82 (across both groups) Sex: 78% female	Individual; 1 × 15 min; clinical research coordinator	None; none	Provision of 5 questions regarding osteoporosis to be given to the PCP	Usual care
Study, follow-up period	Sample size	Patients' characteristic	Intervention Personal component: delivery mode; scope and lengths, educator	Other educational material; follow-up interventions	Other (non-educational) components of intervention	Comparison
Guilera et al. [44], 12 months	Total 745 IG 366 CG 379	Mean age 62 ± 6 (IG), 62 ± 6 (CG) Sex: all female - history of fracture 12% - family history of osteoporosis 49%	Individual; 1 × 15 min; attending physician	Educational leaflet; none	No other components	Usual care
Nielsen et al. [46], 2 years	Total 300 IG 150 CG 150	Median age 63 (IG), 64 (CG) Sex: 89% female	Group (n = 8–12); 4 weekly sessions of 3–4 h; multidisciplinary team: nurses, physiotherapists, dieticians, doctors	None; reinforcement programme: computerised telephone call once a month for 4 months + 2-h brush-up course after 1 year	Medical consultation in osteoporosis outpatient clinic at inclusion (approx. 1 h) and at 3 months (10–15 min)	Usual care
Pekkarinen et al. [47], 10 years	Total 2178 IG 1004 CG 1174	Mean age 65 ± 3 (IG), 65 ± 3 (CG) Sex: all female - history of fracture 21% - bisphosphonate use 2%	Group ($n \approx 15$) and individual; 1-week course[c]; physiotherapists, nutritionists, occupational therapists, podiatric, exercise leaders and research physician	Educational material (mailed twice); 2 review days incl. lectures (3 and 8 years after initial intervention)	No other components	Usual care
Plawecki et al. [36], 8 weeks	Total 69 IG 35 CG 34	Mean age 66 ± 10 (across both groups) Sex 83% female Ethnicity 90% white - osteoporosis diagnosis 33% - previous bone scan 81%	Group (size not described); 8 weekly sessions of 1 h; no information given	Supplemental handouts + binder of resource material for bone health; none	BMD testing in session 1	Usual care*
Rolnick et al. [37], 6 months	Total 695 IG 1 301 IG 2 207	[d] Sex all female Ethnicity 97% Caucasian	Group (size not described); 1 × 2 h; nurse practitioner	None; none	BMD testing in IG 2	Usual care

Table 1 (continued)

Study, follow-up period	Sample size	Patients' characteristics	Intervention Personal component: delivery mode; scope and lengths, educator	other educational material; follow-up interventions	Other (non-educational) components of intervention	Comparison
	CG 187[d]	- history of fracture 8% - SCORE results >6 (i.e. at risk) 71%[e]				
Schousboe et al. [38], 12 months	Total 310 IG 158 CG 152	Mean age 72 ± 8 (IG), 73 ± 8 (CG) Sex: all female - history of fracture 17%	Individual; 1 × 15 min; nurse educator	Two educational brochures; telephone follow-up at 3, 6 and 9 months	BMD report incl. test results and recommendations regarding diagnosis and treatment were sent to PCP of all participants (IG and CG)	Usual care
Tüzün et al. [42], 12 months	Total: 448 IG 226 CG 222	Mean age 62 ± 8 (across both groups) Sex: all female - mean T-score (neck) −2.17	Group (n = 10); 4 quarterly meetings (length not described); no information given	"Starter training kit" incl. bisphosphonate usage guide, osteoporosis training booklet; 4 follow-up visits at 3-month interval (incl. CG)	Four telephone calls reminding patients to read booklet and informing them about the topic of the next educational meeting	Usual care
Yuksel et al. [39], 4 months	Total 262 IG 129 CG133	Median age 61 (IG), 63 (CG) Sex 65% female Ethnicity 61% white - history of fracture 17% - family history of osteoporosis 40% - QUS result indicating low bone mass at heel 47%	Individual; 1 × 30 min; community pharmacists	Osteoporosis brochure and pamphlet; follow-up phone calls at 2 and 8 weeks	QUS measurement + study details and QUS results were sent to PCP	Usual care

All information about patient characteristics relates to IG 1 and IG 2; no demographic details given about CG

BMD bone mineral density, *CG* control group, *IG* intervention group, *PCP* primary care physician, *QUS* quantitative ultrasound, *SCORE* simple calculated osteoporosis risk estimation

[a] The CG in these studies were wait-list CG, i.e. they received the intervention after the study was finished

[b] The differences between intervention and usual care were analysed after 6 months. Then, control subjects also received the interventions to examine whether the intervention effect can be replicated and all patients were followed-up for another 6 months

[c] Including daily activities adding up to 1 ¾ to 5 h a day. Additionally, supervised gym sessions (1–2 h) were offered on 4 days (which were optional)

[d] Control subjects were selected 6 months postintervention by matching potential control subjects to the participants in the intervention groups

[e] The authors did not provide the mean or median age but only the number of patients in four age groups: about 25% of people were aged 54–56, 57–59, 60–62 and 63–65 years, respectively

was low in 5 [33, 37, 39, 41, 47], unclear in 4 [34, 42, 43, 46] and high in 2 studies [35, 38]. In these two trials, the risk of bias was considered to be high as the study investigators relied on patients' self-report (who were not blinded) instead of using more objective measures (e.g. obtaining the relevant data from medical records), which are less prone to bias.

The risk of bias due to incomplete outcome data was low in eight trials [33, 35, 36, 38, 39, 41, 43, 46], while it was considered to be high in the remaining five [34, 37, 42, 44, 47]. Reasons for a high risk of bias include overly high proportions of missing data and a considerable rate of drop-outs in the study groups.

Almost all studies (n = 11) presented all prespecified outcomes (prespecified in the trial register, study protocol or the "Methods" section of the report) and reported non-significant outcomes in the same manner as significant outcomes. In two trials [34, 45, 46], the risk of bias was considered to be high.

As patients, personnel and outcome assessment of subjective and behavioural outcomes could not be blinded in any trial, no study is completely free of bias. Overall, the general risk of bias is considered to be moderate to high in the included trials.

A summary of the risk of bias evaluation is shown in Fig. 2 and detailed risk of bias assessments of each included trial is provided in Appendix B. Blank spaces in the two subgroups of the domain "blinding of outcome assessment" indicate that the trial did not assess any outcomes of the respective outcome group.

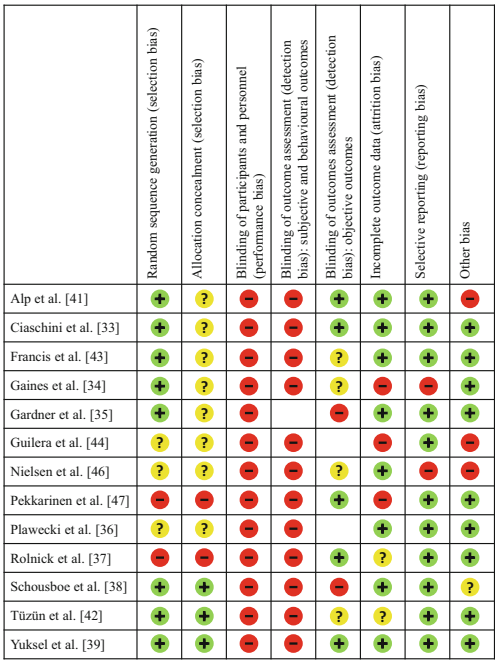

Fig. 2 Summary of the risk of bias assessment (RevMan [48] was used to create this figure) *plus sign*: low risk of bias; *question mark*: unclear risk of bias; *minus sign*: high risk of bias

Study results

A great variety was observed regarding the types of outcomes assessed (Table 2). Eight different primary outcomes were assessed in 11 different trials. Some of these outcomes covered several aspects which were analysed separately in the trials (e.g. the outcome 'appropriate osteoporosis management' included initiation of pharmacological therapy as well as calcium and vitamin D intake). Only two primary outcomes were used in more than one trial: medication adherence[5] (n = 4) and the composite endpoint of dual x-ray absorptiometry (DXA) scan/initiation of pharmacological osteoporosis therapy (n = 2). Two trials [34, 36] did not explicitly distinguish their outcomes as primary and secondary outcomes. Overall, the most common outcomes (primary and secondary) were calcium intake (assessed in six studies) as well as pharmacological treatment and vitamin D (each assessed in five studies).

Collectively, 17 different methods[6] and instruments have been applied to analyse outcomes of interest. Most outcome data has been measured through patients' self-report (questionnaires or interviews). In some studies, outcomes were measured at baseline and at the end of the study period, whereas in others, outcomes were assessed up to five times throughout the study (Table 2).

The outcome 'composite endpoint of BMD testing or initiation of pharmacological treatment'—which was considered in two trials [35, 39]—revealed statistically significant intergroup differences in both of them. The intergroup differences with respect to calcium and vitamin D intake as well as osteoporosis knowledge were found to be statistically significant in favour of the IG in ≥50% of studies analysing these outcomes. In contrast, differences between the IG and the CG regarding pharmacological treatment, medication adherence, physical activity, fractures and QoL were found to be statistically significant in fewer than 50% of trials examining these endpoints. Overall, no clear association between statistically significant results and the delivery mode (group-based vs. individual education), the length or complexity of the educational programme, the sample size, the study duration, the type of outcome (primary vs. secondary outcome) or trials with CG which received educational material could be observed.

Osteoporosis management

Overall, the majority of trials (n = 9) analysed osteoporosis management outcomes.

Two trials [39, 35] had a composite endpoint, defined as the percentage of patients who received a BMD test (DXA scan) or osteoporosis treatment (i.e. a new prescription). Both trials [35, 39] showed statistically significant results in favour of the IG, i.e. the educational programme doubled the number of patients in

[5] Also called compliance or persistence by some authors

[6] Questionnaires and surveys developed by the respective study investigators were counted as one method. In total, self-developed questionnaires were applied in eight trials.

Table 2 Outcomes, assessment methods and times of measurement of included trials

Study	Outcome (assessment method/instrument)	Time of measurement
Alp et al. [41]	Primary: QoL (SF-36) Secondary: physical activity, fractures (questionnaire)	Baseline, 5 weeks, 6 months
Ciaschini et al. [33]	Primary: appropriate osteoporosis management at 6 months incl. pharmacological treatment, calcium and vitamin D intake (patient records, pharmacy data) Secondary: fractures (patient diaries)	6 and 12 months
Francis et al. [43]	Primary: knowledge change (OKAT)	Baseline, 6 weeks
Gaines et al. [34]	Osteoporosis knowledge (FOQ)[a]	Baseline, 1 and 2 years
Gardner et al. [35]	Primary: composite endpoint: percentage of patients in whom osteoporosis was addressed, i.e. DXA scan or bisphosphonate therapy (telephone interview)	6 months
Guilera et al. [44]	Primary: adherence (Morisky test) Secondary: HRQoL (EuroQoL)	Baseline, 3 and 12 months
Nielsen et al. [46]	Primary: adherence (questionnaire) Secondary: osteoporosis knowledge (PAVIOS questionnaire)	Baseline (knowledge only), 3, 12 and 24 months
Pekkarinen et al. [47]	Primary: hip fracture incidence (National Hospital Discharge Registers, death certificates from the National Cause of Death Register) Secondary: bone-related lifestyle changes incl. medication, exercise, calcium and vitamin D intake, smoking (questionnaire)	Baseline, 2, 5, 8 and 10 years
Plawecki et al. [36]	Dietary intake incl. calcium and vitamin D (CFFFQ, 24-h recalls using the US Department of Agriculture multipass system of diet recall)[a]	1, 4 (IG only) and 8 weeks
Rolnick et al. [37]	Primary: pharmaceutical and lifestyle changes related to osteoporosis incl. initiation of drug therapy, exercise, calcium and vitamin D intake (mailed survey, prescription data from computerised pharmacy records, patient records)	Baseline (IG only), 6 months
Schousboe et al. [38]	Primary: initiation of and persistence with HRT or other antiresorptive therapy (telephone survey) Secondary: calcium intake, exercise frequency (telephone survey)	12 months
Tüzün et al. [42]	Primary: treatment compliance and persistence (patients' self-report) Secondary: vertebral and non-vertebral fractures (patients' self-report), QoL (QUALEFFO-41 questionnaire)	Baseline, 3, 6, 9 and 12 months
Yuksel et al. [39]	Primary: composite endpoint: BMD test with central DXA or initiation of pharmacological treatment (patients' self-report, copies of BMD measurements from PCP, copies of prescription from pharmacy) Secondary: each component of the primary endpoint, total daily calcium and vitamin D intake (patients' self-report), osteoporosis knowledge (FOQ), changes in generic health status (SF-12), osteoporosis-specific QoL (OPTQoL)	Baseline (calcium and vitamin D intake only), 4 months

CFFQ Calcium-Focused Food Frequency Questionnaire, *EuroQoL* generic health-related QoL questionnaire developed by the EuroQoL group, *FOQ* Facts on Osteoporosis Quiz, *HRQoL* health-related QoL, *HRT* hormone replacement therapy, *IG* intervention group, *OKAT* Osteoporosis Knowledge Assessment Test, *OPTQoL* Osteoporosis-Targeted Quality of Life questionnaire, *PAVIOS* Patienters Viden om Osteoporose (patients' knowledge of osteoporosis), *SF-12/SF-36* 12-item/36-item Short-Form Health Survey, *QUALEFFO-41* 41-Item Quality of Life European Foundation for Osteoporosis questionnaire, *QoL* Quality of Life

[a] The authors assessed multiple outcomes (of which some were not considered in this review) and did not differentiate between primary and secondary outcomes

whom osteoporosis was addressed (i.e. patients received a DXA scan or bisphosphonate therapy) compared to usual care (Table 3). In the trial of Yuksel et al. [39], the differences were driven by BMD tests, whilst in the trial of Gardner et al. [35], 47% of patients in whom osteoporosis was addressed received both (BMD testing and pharmacological treatment), 33% only had a BMD test and 20% received bisphosphonate therapy only.

The percentage of patients who received a DXA scan was analysed as a secondary outcome in Yuksel et al. [39]. A BMD test with DXA was performed in 22% of the IG patients and in 10% of the CG patients (p = 0.01, absolute difference 12%, 95% CI 3 to 21%).

Pharmacological osteoporosis treatment was examined in five trials [33, 37–39, 47]. Overall, the differences between the IG and the CG were statistically significant in favour of the IG in four out of nine outcomes (Table 3). When this parameter was restricted to the three trials [33, 37, 39] that used patient records or pharmacy data to collect outcome data, the findings regarding pharmacological treatment still remain inconsistent.

Medication adherence, compliance and/or persistence were analysed in four trials [38, 42, 44, 46]. The outcome definitions as well as the inclusion criteria with respect to osteoporosis medication varied considerable across studies. The results of these trials are summarised in Table 3 (except those of

Table 3 Differences in pharmacological treatment and medication adherence at the end of the follow-up

Differences in the composite endpoint (BMD test and/or pharmacological treatment) at the end of follow-up						
Study	Outcome		IG	CG	Abs. diff. (95% CI)	*P* value
Gardner et al. [35]	Percentage of patients in whom osteoporosis was addressed, i.e. DXA scan or bisphosphonate therapy		42%	19%	23% (3; 43%)	0.04
Yuksel et al. [39]	BMD test with central DXA or initiation of pharmacological treatment		22%	11%	11% (2; 20%)	0.02
Differences in pharmacological treatment at the end of follow-up						
Study	Outcome		IG	CG	Abs. diff. (95% CI)	*P* value
Ciaschini et al. [33]	Patients receiving pharmacological treatment (incl. alendronate, risedronate, raloxifene)	T-score <−2.5[a]	56%	27%	29% (11; 47%)	<0.05
		T-score −2.5 to −1[a]	41%	16%	25% (5; 45%)	<0.05
	Patients taking oestrogen/progestin		13%	2%	11% (4; 18%)	<0.05
Pekkarinen et al. [47]	Use of oestrogen		12%	14%	−2% (−5; 1%)	0.18
	Use of bisphosphonates		11%	9%	2% (−1; 5%)	0.43
	Use of calcitonin		1%	<1%	1% (0; 2%)	0.04
Rolnick et al. [37]	Initiation of HRT		9%[b]	12%	−3% (−8; −2%)	0.25
	Initiation of alendronate or raloxifene		5%[b]	0%	5% (3; 7%)	<0.01
Schousboe et al. [38]	Initiation of antiresorptive drug therapy		25%	22%	3% (−13; 13%)	>0.05
Yuksel et al. [39]	Patients receiving a new prescription (incl. any bisphosphonate, nasal calcitonin, raloxifene, teriparatide, hormone therapy)		5%	2%	3% (−1; 7%)	0.30
Differences in medication adherence at the end of the follow-up						
Study	Outcome		IG	CG	Abs. diff. (95% CI)	*P* value
Guilera et al. [44]	Proportion of patients showing high adherence		47%	53%	−6% (−2; 14%)	0.38
Nielsen et al. [46]	Adherence to pharmacological therapy		92%	80%	12% (4; 20%)	0.01
Schousboe et al. [38]	Patients who are still on antiresorptive therapy		16%	22%	−6% (−3; 15%)	>0.05

Abs. diff. absolute difference, *BMD* bone mineral density, *CG* control group, *CI* confidence interval, *DXA* dual x-ray absorptiometry, *HRT* hormone replacement therapy, *IG* intervention group

[a] Analyses were done separately for patients with osteoporosis and osteopenia

[b] Relates to the pooled data of IG 1 and IG 2

Tüzün et al. [42] who used a different approach[7] of outcome measurement without reaching statistical significance. Only one trial [46] reported a statistically significant higher proportion of adherent patients in the IG. When comparing the adherence rates across trials, a substantial variation can be found: the proportion of adherent patients varied between 16 and 92% in the IG and between 22 and 80% in the CG.

Lifestyle modifications

Calcium intake was assessed in six trials [33, 36–39, 47] with almost all showing a significantly higher proportion of patients taking calcium in the IG compared to the CG. Detailed results of this outcome are shown in Table 4 (except those of Plawecki et al. [36] who used a different approach of outcome measurement[8] without demonstrating statistically significant intergroup differences).

Vitamin D intake was evaluated in five trials. [33, 36, 37, 39, 47] Three [33, 37, 47] out of these five studies (60%) reported a significantly higher proportion of patients taking vitamin D in the IG compared to the CG. Detailed results of this outcome are shown in Table 4 (except those of Plawecki et al. [36] who used a different approach of outcome measurement[9] without demonstrating statistically significant intergroup differences).

Results for the outcomes physical activity and changes in smoking behaviour are shown in Table 4.

Alp et al. [41] also assessed physical activity in both study groups but did not analyse it statistically. Therefore, their results are not shown in Table 4. They report that 74% in the IG participated in regular physical activity (balance and weight-bearing exercises two or three times a week), while no behavioural changes occurred in the CG. However, it is important to note that the participants in the CG were specifically instructed to maintain their sedentary lifestyle.

[7] In the other trials, the IG and the CG were analysed separately, i.e. it was calculated how many of the IG and the CG patients were adherent. In contrast, Tüzün et al.[42] did not assess how many patients in each group were adherent/non-adherent, but looked at all adherent/non-adherent patients (i.e. of the whole study population) and then assessed how many of the adherent/non-adherent patients were from the IG and how were part of the CG.

[8] They measured the average calcium intake in milligrams.

[9] They measured the average vitamin D intake in International Units (IU).

Table 4 Differences in lifestyle modifications at the end of the follow-up

Differences in calcium intake at the end of the follow-up						
Study	Outcome		IG	CG	Abs. diff. (95% CI)	*P* value
Ciaschini et al. [33]	Patients taking the recommended amount of calicum[a]		54%	20%	34% (22; 46%)	<0.05
Pekkarinen et al. [47]	Patients who started using calcium supplements during the 10 years of the study duration		24%	23%	1% (−3; 5%)	0.03
	Patients who maintained their calcium supplement use during the 10 years of the study duration		35%	29%	6% (2; 10%)	
	Patients who stopped using or never used calcium supplements during the 10 years of the study duration		41%	47%	−6% (−2; −10%)	
Rolnick et al. [37]	Patients reporting increased calcium intake		63%[b]	51%	12% (4; 20%)	<0.01
Schousboe et al. [38]	Patients reporting increased daily calcium intake		59%	39%	20% (9; 31%)	<0.05
Yuksel et al. [39]	Additional patients reaching total daily calcium intake of 1500 mg (diet and supplements)[c]		30%	19%	11% (1; 21%)	<0.05
Differences in vitamin D intake at the end of the follow-up						
Study	Outcome		IG	CG	Abs. diff. (95% CI)	*P* value
Ciaschini et al. [33]	Patients taking the recommended amount of vitamin D[a]		33%	20%	13% (1; 25%)	<0.05
Pekkarinen et al. [47]	Patients who started using vitamin D supplements during the 10 years of the study duration		32%	29%	3% (−1; 7%)	<0.01
	Patients who maintained their vitamin D supplements use during the 10 years of the study duration		47%	40%	7% (3; 11%)	
	Patients who stopped using or never used vitamin D supplements during the 10 years of the study duration		21%	31%	−10% (−14; −6%)	
Rolnick et al. [37]	Patients reporting increased vitamin D intake		43%[b]	24%	19% (12; 26%)	<0.01
Yuksel et al. [39]	Additional patients reaching a total daily vitamin D intake of 800 IU (diet and supplement)[d]		19%	17%	2% (−7; 11%)	>0.05
Differences in physical activity at the end of the follow-up						
Study	Outcome		IG	CG	Abs. diff. (95% CI)	*P* value
Pekkarinen et al. [47]	Patients doing aerobic exercises lasting ≥30 min	0–1 times/week	7%	7%	0% (N/A)	0.80
		2–4 times/week	35%	33%	2% (−3; 7%)	
		5–7 times/week	58%	60%	−2% (−8; 4%)	
Rolnick et al. [37]	Patients reporting increased exercise		53%[a]	47%	6% (−2; 14%)	0.13
Schousboe et al. [38]	Patients reporting increased frequency of exercise		34%	21%	13% (3; 23%)	<0.05
Differences in smoking at the end of the follow-up						
Study	Outcome		IG	CG	Abs. diff. (95% CI)	*P* value
Pekkarinen et al. [47]	Change in smoking over 10 years	Stopped smoking	4%	5%	−1% (−3; 1%)	<0.01
		No smoking	91%	86%	5% (2; 8%)	
		continued/started smoking	5%	9%	−4% (−6; −2%)	

Abs. diff. absolute difference, *CG* control group, *CI* confidence interval, *IG* intervention group, *N/A* not available/applicable

[a] Amount recommended in the 2002 clinical practice guideline for osteoporosis in Canada

[b] Relates to the pooled data of IG 1 and IG 2

[c] That is, the number of additional patients with a total daily calcium intake of 1500 mg after 4 months, who had a baseline calcium intake of <1500 mg (1500 mg is the recommended dietary allowance)

[d] That is, the number of additional patients with a total daily vitamin D intake of 800 IU after 4 months, who had a baseline vitamin D intake of <800 IU (800 IU is the recommended dietary allowance)

Fractures

Fractures were assessed in four studies [33, 41, 42, 47]. Pekkarinen et al. [47] assessed hip fracture incidence as a primary outcome based on data from the National Hospital Discharge Register in Finland. During the 10-year follow-up, 12 women (1%) in the IG and 29 women (3%) in the CG sustained a hip fracture. This difference was statistically significant (p = 0.04, absolute difference: 2%, 95% CI 1 to 3%). After adjusting for baseline differences, the risk of hip fractures was reduced by 55% with the educational intervention. When any other fractures were also considered, significantly less women in the IG were admitted to hospital (59 (6%) vs. 95 (8%), p = 0.045). In the remaining trials, any differences were not statistically significant (p > 0.05).

Table 5 Differences in osteoporosis knowledge at the end of the follow-up

Study	Highest possible score	Outcome		IG	CG	*P* value
Francis et al. [43]	20	Mean knowledge score		13	10	<0.01
Gaines et al. [34]	20	Mean knowledge score	Men	12	11	>0.05
			Women	14	14	>0.05
Nielsen et al. [45] [46]	27	Median knowledge score		24	22	<0.01
Yuksel et al. [39]	N/A	Percentage of patients scoring correctly in the knowledge survey		57%	54%	>0.05

CG control group, *IG* intervention group

Overall, the trial [47] with a long-term follow-up showed a statistically significant decrease in fractures in elderly women, while trials [33, 41, 42] with a short-term follow-up did not show a clear effect.

Osteoporosis knowledge

Osteoporosis knowledge was assessed in four trials [34, 39, 43, 46]. All four trials used multiple-choice questionnaires with true-false schemes, consisting of 20 to 27 questions. Although Gaines et al. [34] and Yuksel et al. [39] both used the "Facts on Osteoporosis Quiz" (FOQ), the results were presented in a completely different manner: Gaines et al. [34] reported the mean knowledge scores of the two study groups, while Yuksel et al. [39] stated the percentage of patients answering the questionnaire correctly, making direct comparison difficult.

Table 5 summarises the differences in osteoporosis knowledge between the IG and the CG at the end of the follow-up. In two [43, 45, 46] out of four trials (50%), the analyses showed significantly better knowledge scores in the IG at the end of the follow-up compared with the CG.

Quality of life

QoL was assessed in four trials (Table 6) [39, 41, 42, 44]. One of those assessed QoLs as a primary outcome and reported significant improvements in all domains of the SF-36 in the IG compared to the CG [41]. In the other three trials, there were no statistically significant differences [39, 42, 44].

CG control group, *IG* intervention group, *SF-36* 36-Item Short Form Health Survey, *QUALEFFO-41* 41-item Quality of Life European Foundation for Osteoporosis questionnaire, *OPTQoL* Osteoporosis-Targeted Quality of Life questionnaire

Yuksel et al. [39] additionally assessed the generic health status (SF-12). The mean mental and physical component scores were similar across groups at the end of the follow-up ($p = 0.97$ and $p = 0.98$, respectively).

Table 6 Differences in QoL at the end of the follow-up

Study	Outcome		IG	CG	*P* value
Alp et al. [41]	Mean change in SF-36 scores from baseline to 6 months of follow-up	SF-36PF (physical functioning)	25	−1	<0.01
		SF-36PRL (physical role limitations)	44	−24	<0.01
		SF-36SF (social functioning)	14	−1	<0.01
		SF-36MH (mental health)	17	−1	<0.01
		SF-36 vitality	22	5	<0.01
		SF-36P (pain)	23	−7	<0.01
		SF-36GHP (general health perceptions)	9	−4	<0.05
		SF-36ERL (emotional role limitations)	39	−1	<0.01
Tüzün et al. [42]	Mean QUALEFFO-41 score		33	35	0.17
Yuksel et al. [39]	Mean OPTQoL score	Physical functioning	72	72	0.99
		Adaptation	67	70	0.36
		Fears	80	79	0.69

The results of Guilera et al. [44] could not be included in this table as the results were only presented graphically

Discussion

Summary of main results

This systematic review assessed 13 different trials evaluating the effects of patient education on osteoporosis prevention and treatment results. In summary, patient education resulted in improved osteoporosis management (i.e. earlier BMD testing or initiation of pharmacological treatment), calcium and vitamin D intake as well as osteoporosis knowledge in more than 50% of the included studies. In contrast, differences between the IG and the CG regarding pharmacological treatment, medication adherence, physical activity, fractures and QoL were improved in fewer than 50% of trials. No clear association could be found between statistically significant results and characteristics of the intervention such as the delivery mode (group-based vs. individual education), the length or complexity of the educational programme. Because of these inconsistent results and moderate to high risks of bias of the included studies, a conclusive statement about the effects of patient education on osteoporosis prevention and treatment results cannot be drawn, and the results need to be interpreted with caution (Table 7).

The inconsistency (heterogeneity) across the included trials with respect to several aspects (e.g. design of the interventions) made it difficult to assess why some education programmes led to improvements in the outcomes of interest, while others did not. In cases of large or unexplained inconsistency, the GRADE group even recommends rating down the quality of the overall evidence which would weaken the potential conclusions deducible from this review [49]. However, the transparent disclosure of methodological drawbacks as summarised below is important for balancing the principal opportunities and risks associated with patient education in osteoporosis prevention (Table 8).

Limitations and risks of bias of included trials

The overall risk of bias of the included trials was graded as moderate to high due to methodological limitations especially in the areas of randomisation processes, blinding of participants as well as personnel and outcome assessment.

As blinding of participants and personnel may not be feasible in educational intervention trials, it introduces a high risk of bias. Therefore, it is even more important to ensure objective and blinded outcome assessment where applicable [32, 50–52].

Certainly, outcomes such as QoL cannot be assessed objectively due to their subjective nature. Additionally, outcomes regarding lifestyle changes are difficult to assess objectively as the only objective means would be direct observation, which is not feasible. The risk of bias could be reduced, if patient surveys and interviews are conducted by trained and blinded interviewers, and if validated questionnaires/instruments are used more increasingly [32, 50, 51].

Several other limitations of the included trials need to be considered. First of all, there was considerable variance in how outcomes were defined and measured. For example, in some trials, calcium intake was assessed without differentiating between dietary sources of calcium and calcium supplements [33, 37–39], while in others, researchers focused on supplementary or dietary calcium intake only [47]. Similar issues exist for other outcomes such as vitamin D or medication adherence. A further reason for the variance of outcome measurement was a broad range of assessment methods (17 methods/instruments) used in the included trials, including the use of non-validated questionnaires or questionnaires developed by the study investigators [33, 35–38, 41, 42, 46, 47].

To allow for direct comparison and meta-analysis of study results, it is important for researchers to find consensus regarding the terminology and definition of outcome measures as well as on the most appropriate assessment methods for educational intervention trials. For instance, Madureira et al. [53] provide an overview of osteoporosis-specific QoL questionnaires, which may help investigators to select the most appropriate questionnaire for their trials.

Secondly, some reports lacked important information about the study population or the intervention, and the presentation of outcome data varied across studies. For example, important information about patients' characteristics (e.g. existing osteoporosis risk factors) or about the intervention (e.g. about the educator, group size, scope and length) were not reported in all included trials. Heterogeneous reporting and limited information about specific aspects in some trials made direct comparisons at least difficult, if not impossible.

Third, some trials had multiple primary endpoints [33, 37, 38, 41] or did not differentiate between primary and secondary outcomes [34, 36]. Multiple analyses of the same data, without adjustment of sample size, are at risk for type I error (false-positive rate) [54]. However, chronic diseases such as osteoporosis and their management are multifaceted and the usage of appropriate statistical methods is important. Appropriate statistical methods include the frequentist/Bayesian approach, the Bonferroni or the Hochberg procedure and others [55–57]. None of the included trials with multiple primary endpoints considered the related issues or described any statistical methods undertaken to address them.

Fourth, the follow-up durations of most trials may be an issue of concern because more than half of the studies had follow-up periods of 6 months or less. As a result, the short follow-up times may limit the ability to detect important long-term effects of patient education. In particular, clinically relevant behavioural changes may require longer periods to be achieved, or in the case of significant behavioural changes observed during short study periods, a

long-term evaluation is needed as some benefits may fade as time passes [58].

Fifth, the external validity of the included trials may be limited, which was acknowledged by the majority of authors. The study populations of the included trials may not be representative of osteoporosis populations due to specific settings and recruitment processes applied.

Finally, only one study assessing the incidence of osteoporotic fractures as a primary endpoint could be identified. Although the result of this trial [47] showed a significant reduction of hip fractures, this has to be interpreted with caution due to high risks of selection, performance and attrition bias.

Results of additional conference abstracts

During the literature search, conference abstracts of two RCTs were found of which the full text has not been published yet. Lin et al. [59] conducted a trial to evaluate an osteoporosis education programme with a 1-year follow-up. Participants were postmenopausal osteoporotic women (n = 120), and the educational intervention was delivered either individually or in group sessions. At the end of the follow-up, participants of the IG were more compliant than those in the CG (no intervention) [59]. In the second trial, McLeod et al. [60, 61] assessed the impact of a theory-based osteoporosis education and screening programme on calcium and vitamin D intake in men and women aged 50 years and above (n = 203). At the 6-month follow-up, they observed a statistically significant difference (p = 0.03) in calcium and vitamin D intake between the IG and the CG (usual care).

Comparison with other reviews

The results of this review are in line with the findings of a systematic review conducted by Jensen et al. [25], who investigated the effectiveness of multifaceted osteoporosis group education, including RCTs and observational studies. The authors reported that group education interventions may have a positive effect on lifestyle changes, adherence, knowledge and QoL, but no clear conclusions could be drawn from the included trials. In contrast, Smith et al. [26], who conducted a systematic review about healthcare professional-led education, found that eight out of nine trials showed improved adherence to osteoporosis medication. However, the review was based on different levels of evidence (i.e. RCTs, two quasi-experimental trials, and comparative studies).

Four other systematic reviews [24, 27, 29, 31] that investigated the effects of multiple interventions to improve osteoporosis treatment varied in some way in their inclusion criteria from this review, but their results were also consistent with our findings.

Strength and limitations

To our knowledge, this is the first comprehensive systematic review that focuses on the effects of patient education only, was not restricted to publication date, assessed multiple endpoints based on evidence-based recommendations in clinical guidelines and was based on RCTs only. Noteworthy, the RCTs included in the analysis undertook a critical assessment of their methodological quality.

Besides these strengths, this review also has some limitations. First, the search was restricted to specific languages. Although a publication bias could not be completely ruled out, our literature search identified no relevant articles in any other language, and no study was excluded due to language restrictions only. Secondly, study heterogeneity made direct comparison of interventions difficult and precluded any statistical aggregation and meta-analysis of study results.

Conclusions

To summarise, this review indicates that it is still unclear whether patient education is beneficial and whether it has a significant and clinically important impact on osteoporosis management results. Educational programmes for osteoporosis require further investigation within the context of well-conducted RCTs with longer follow-up periods (at least 4 or 5 years) and larger sample sizes. Furthermore, future trials should aim to recruit higher proportions of men because a substantial number of men are affected by osteoporosis.

The study methodology of future studies needs to be improved to minimise the risk of bias. Future studies need to apply adequate randomisation procedures and improve the description thereof. Additionally, future trials should include standardised, adequate and detailed descriptions of the education programme, the participants and the outcome measures. For instance, Jensen et al. [62] provide a comprehensive description of the educational programme, which may provide a good example of how to describe educational programmes in future studies. Researchers also need to find consensus on the terminology and definition of outcomes as well as on the most appropriate assessment methods and instruments. Several initiatives started developing standardised outcome sets, which will facilitate comparability of future RCTs (COMET Initiative, ICHOM)[10] Where available, researchers should refer to already existing guidelines and use standardised and validated instruments.

Compliance with ethical standards

Conflict of interest None.

[10] COMET = Core Outcome Measures in Effectiveness Trials; ICHOM = International Consortium for Health Outcomes Measurement

Appendix

Table 7 List of Excluded Studies

Study	Primary reason for exclusion
Ashe, M./Khan, K./Guy, P./Kruse, K./Hughes, K. et al.: Wristwatch-Distal Radial Fracture as a Marker for Osteoporosis Investigation: A Controlled Trial of Patient Education and a Physician Alerting System. In: Journal of Hand Therapy 2004: 17 (3), 324–328.	Intervention: no patient education, but patient notification and not including a personal part
Ashe, M. C./McKay, H. A./Janssen, P./Guy, P./Khan, K. M.: Improving Osteoporosis Management in at-Risk Fracture Clinic Patients. In: Journal of the American Geriatrics Society 2005: 53 (4), 727–728.	Article is a letter to the editor
Colon-Emeric, C.S./Lyles, K.W./House, P./Levine, D.A./Schenck, A.P. et al.: Randomised Trial to Improve Fracture Prevention in Nursing Home Residents. In: The American Journal of Medicine 2007: 120 (10), 886–892.	Intervention: targeted at nursing home staff, not at patients
Cranney, A./Lam, M./Ruhland, L./Brison, R./Godwin, M. et al.: A Multifaceted Intervention to Improve Treatment of Osteoporosis in Postmenopausal Women with Wrist Fractures: a Cluster Randomised Trial. In: Osteoporosis International 2008: 19 (12), 1733–1740.	Intervention: does not include a personal part, only includes written material
Davis, J.C./Guy, P./Ashe, M.C./Liu-Ambrose, T./Khan, K.: HipWatch: Osteoporosis Investigation and Treatment after a Hip Fracture: A 6-month Randomised Controlled Trial. In: The Journals of Gerontology 2007: 62 (8), 888–891.	Intervention: does not include a personal part, only includes written material
Delafuente, J.C./Weakley, D.F.: Can an Educational Program for Residents of Assisted Living Facilities Improve Drug Utilisation for Osteoporosis? In: The Consultant Pharmacist 2005: 20 (2), 137–140.	Patients: insufficient information about the participants (no information regarding their age, diagnosis of osteoporosis or history of fragility fractures)
Grahn Kronhed, A.-C./Blomberg, C./Lofman, O./Timpka, T./Moller, M.: Evaluation of an Osteoporosis and Fall Risk Intervention Program for Community-Dwelling Elderly. A Quasi-experimental Study of Behavioural Modifications. In: Ageing Clinical and Experimental Research 2006: 18 (3), 235–241.	Intervention: population-based intervention is primarily targeted at personnel of nursing homes, municipal home-help service units, associations for retired persons, study circles and sport clubs as well as the general population; individual part only includes written material
Lai, Pauline Siew Mei/Chua, S.S./Chan, S.P.: Impact of Pharmaceutical Care on Knowledge, Quality of Life and Satisfaction of Postmenopausal Women with Osteoporosis. In: International Journal of Clinical Pharmacy 2013: 35 (4), 629–637.	Full text not available
Lin H./Chen X./Zhu X./Qian C.: The Effects of Health Management Intervention on Postmenopausal Osteoporosis Women Treatment. In: Osteoporosis International 2012: 23, 149–150.	Conference Abstract, no full text available
Majumdar, S.R./Beaupre, L.A./Harley, C.H./Hanley, D.A./Lier, D.A. et al.: Use of a Case Manager to Improve Osteoporosis Treatment After Hip Fracture: Results of a Randomised Controlled Trial. In: Archives of Internal Medicine 2007: 167 (19), 2110–2115.	Intervention: no patient education in the narrow sense, but case management
Manios/Y./Moschonis, G./Katsaroli, I./Grammatikaki, E./Tanagra, S.: Changes in Diet Quality Score, Macro- and Micronutrients Intake Following a Nutrition Education Intervention in Postmenopausal Women. In: Journal of Human Nutrition and Dietetics: The Official Journal of the British Dietetic Association 2007, 20 (2), 126–131.	Intervention: mainly focused on nutrition and participants are provided with fortified food and supplements.
McDonough, R.P./Doucette, W.R./Kumbera, P./Klepser, D.G.: An Evaluation of Managing and Educating Patients on the Risk of Glucocorticoid-induced Osteoporosis. In: Value in Health 2005: 8 (1), 24–31.	Patients: includes patients aged 18 years and older
McLeod K./Johnson S./Rasali D.: Impact of a Theory-based Osteoporosis Education Intervention and BMD Screening on Calcium and Vitamin D Intake in Older Men and Women. In: Journal of Bone and Mineral Research 2013: 28 (Suppl. 1), n .pag.	Conference Abstract, no full text available
McLeod K.M./Johnson S.C, Rasali D./Verma A.: Impact of a Theory-based Osteoporosis Education Intervention on Calcium and Vitamin D Supplement Intake in Older Adults: A Randomised Controlled Trial. In: Osteoporosis International 2012: 23 (Suppl. 2), S233.	Conference Abstract, no full text available
Prihar, B.J./Katz, S.: Patient Education as a Tool to Increase Screening for Osteoporosis. In: Journal of the American Geriatrics Society 2008: 56 (5), 961–962.	Article is a letter to the editor
Roux, S./Beaulieu, M./Beaulieu, M.-C./Cabana, F./Boire, G.: Priming Primary Care Physicians to Treat Osteoporosis after a Fragility Fracture: an Integrated Multidisciplinary Approach. In: The Journal of Rheumatology 2013: 40 (5), 703–711.	Intervention: primarily targeted at physicians
Silverman, S.L./Nasser, K./Nattrass, S./Drinkwater, B.: Impact of Bone Turnover Markers and/or Educational Information on Persistence to Oral Bisphosphonate	

Table 7 (continued)

Study	Primary reason for exclusion
Therapy: a Community Setting-based Trial. In: Osteoporosis International 2012: 23 (3), 1069–1074.	Intervention: focusses on reporting of bone turnover marker results and only includes written educational material
Solomon, D.H./Katz, J.N./Finkelstein, J.S./Polinski, J.M./Stedman, M. et al.: Osteoporosis Improvement: A Large-scale Randomised Controlled Trial of Patient and Primary Care Physician Education. In: Journal of Bone and Mineral Research 2007: 22 (11), 1808–1815.	Intervention: patient intervention does not include a personal part, only includes written material
Warriner, A.H./Outman, R.C./Feldstein, A.C./Roblin, D.W./Allison, J.J. et al.: Effect of Self-referral on Bone Mineral Density Testing and Osteoporosis Treatment. In: Medical Care 2014: 52 (8), 743–750.	Intervention: focusses on self-referral and the educational intervention does not include a personal part
Winzenberg, T./Oldenburg, B./Jones, G.: Bone Density Testing: An Under-utilised and Under-researched Health Education Tool for Osteoporosis Prevention? In: Nutrients 2010: 2 (9), 985–996.	Patients: includes patients aged between 25 and 44 years

Table 8 Risk of Bias Assessment of Included Studies (The table has been adapted from Higgins et al. [23])

Alp et al. [32]		
Domain	Support for judgement	Author's judgement
Random sequence generation (selection bias)	Quote: "Simple randomization was done using a computer-generated table of random numbers."	Low risk
Allocation concealment (selection bias)	Comment: Insufficient information to permit judgement of low or high risk, as a description of the concealment method is not provided.	Unclear risk
Blinding of participants and personnel (performance bias)	Quote: "In this single-blind study, an independent researcher gave the questionnaires and did the outcome measurement." Comment: Participants and personnel were not blinded. As most outcomes in this trial are subjective or behavioural outcomes, they are likely to be influenced by the lack of blinding.	High risk
Blinding of outcome assessment (detection bias) (subjective and behavioural outcomes)	Quote: "In this single-blind study, an independent researcher gave the questionnaires and did the outcome measurement." Comment: Although an independent researcher did the outcome measurement, the outcomes were assessed by patients via questionnaires. As patients were not blinded and these outcomes (e.g. physical activity, QoL), are behavioural or highly subjective, they are at high risk of bias.	High risk
Blinding of outcome assessment (detection bias) (objective outcomes)	Comment: For objective outcomes the risk of bias is low as the outcome assessor was blinded.	Low risk
Incomplete outcome data (attrition bias)	Quote: "Three subjects in group 1 and two subjects in group 2 were lost to follow-up" Comment: The attrition rate is reasonably low (12% in the IG, 8% in the CG) and comparable in both groups.	Low risk
Selective reporting (reporting bias)	Comment: All outcomes pre-specified in the methods section of the publication have been reported in the pre-specified way in the results section; non-significant results have been reported in the same manner as significant results and in a very detailed way.	Low risk
Other bias	Quote: "Fifty sedentary women […] were selected […] according to their […] T score of dual-energy x-ray absorptiometry (DEXA) as the inclusion criteria. […] Axial (lumbar 1–4 and femur neck) bone mineral density (BMD) measurements were done at baseline by DEXA […]." Comment: The BMD measurement was conducted before randomisation to ensure that women fulfil the inclusion criteria and are eligible for the study. As patients are likely to know their results of the BMD test, this knowledge might have an impact on their behaviour and thus it could enhance or diminish the effect of the randomised intervention.	High risk
Ciaschini et al. [24][i] [51] (registered at ClinicalTrials.gov: ID: NCT00465387)		
Domain	Support for judgement	Author's judgement
Random sequence generation (selection bias)	Quote (protocol, published report): "Eligible patients were randomised using a computer generated randomization scheme under supervision of the study biostatistician, […]."	low risk
Allocation concealment (selection bias)	Comment: Insufficient information to permit judgement of low or high risk, as a description of the concealment method is not provided and it	Unclear risk

Table 8 (continued)

	remains unclear whether or not the randomisation scheme has been concealed.	
Blinding of participants and personnel (performance bias)	Quote (trial register): "Masking: Open label" Quote (published report): "Patients, treating physicians and outcome assessors could not be blinded to the fact that patients were participating in an osteoporosis improvement study." Comment: The outcomes are likely to be influenced by this lack of blinding as they are subjective or behavioural outcomes.	High risk
Blinding of outcome assessment (detection bias) (subjective and behavioural outcomes)	Quote (published report): "Patients, treating physicians and outcome assessors could not be blinded to the fact that patients were participating in an osteoporosis improvement study." Quote (published report): "The lack of blinding of the outcomes assessors could result in bias such as overestimation of the impact of the intervention."	High risk
Blinding of outcome assessment (detection bias) (objective outcomes)	Quote (published report): "The lack of blinding of the outcomes assessors could result in bias such as overestimation of the impact of the intervention. However, the primary source of data collection was the administrative data obtained from the Group Health Centre Electronic Medical Record." Comment: In the case of the objective outcomes the outcome measurement is not likely to be influenced by the lack of blinding as the measurement was based on medical records.	Low risk
Incomplete outcome data (attrition bias)	Quote (published report): "201 patients were recruited […]. One hundred seventy six patients (88%) completed the study. […] No statistically significant differences were detected […] in losses due to death and follow-up." Quote (published report): "The analysis was by intention to treat."	Low risk
Selective reporting (reporting bias)	Comment: All outcomes pre-specified in the study protocol have been reported in the pre-specified way in the published report, and non-significant outcomes have been reported in the same manner as significant outcomes.	Low risk
Other bias	Comment: No other sources of bias could be identified.	Low risk
Francis et al. [34]		
Domain	Support for judgement	Author's judgement
Random sequence generation (selection bias)	Quote: "Participants […] were randomly allocated to either 'control' or 'intervention' group using a computer-generated random number list."	low risk
Allocation concealment (selection bias)	Comment: Insufficient information to permit judgement of low or high risk, as the method used for allocation concealment is not described.	Unclear risk
Blinding of participants and personnel (performance bias)	Quote: "A further limitation […] is that the wait list control group were not blinded to their group assignment and it is possible that this may have biased the results in favour of the intervention group." Comment: Blinding of participants and personnel is not feasible due to the nature of the intervention and the outcomes are likely to be influenced by this lack of blinding as they are mainly subjective or behavioural outcomes.	High risk
Blinding of outcome assessment (detection bias) (subjective and behavioural outcomes)	Comment: No information given regarding the blinding of outcome assessment. However, the subjective and behavioural outcomes are self-reported by the participants who are not blinded and thus a high risk of bias exists.	High risk
Blinding of outcome assessment (detection bias) (objective outcomes)	Comment: No information given regarding the blinding of outcome assessment and thus, the risk of bias remains unclear.	Unclear risk
Incomplete outcome data (attrition bias)	Quote: "The 'last value carried forward' approach was used for the missing data, that is, the participant's previous score was used when the follow-up data was missing (n = 27; 14% of the sample: 14 participants from the intervention group and 13 from the control group)" Comment: As the attrition rate is reasonably low and missing outcome data is balanced in numbers across the intervention and control group, the risk of bias is low. The 'last observation varied forward' approach is considered to be an appropriate method to deal with missing outcome data in this case, as the data of interest is knowledge scores, which are unlikely to change (neither improve nor deteriorate) when dropping out of an educational trial.	Low risk
Selective reporting (reporting bias)	Comment: All outcomes pre-specified in the methods section of the publication have been reported in the pre-specified way in the results section; non-significant results have been reported in the same manner as significant results.	Low risk
Other bias	Comment: No other sources of bias could be identified.	Low risk

Table 8 (continued)

Gaines et al. [25]		
Domain	Support for judgement	Author's judgement
Random sequence generation (selection bias)	Quote: "Participants were assigned randomly (1:1 numbered envelope allocation)."	Low risk
Allocation concealment (selection bias)	Comment: Insufficient information: although the use of envelopes is mentioned, it remains unclear whether they were opaque and sealed.	Unclear risk
Blinding of participants and personnel (performance bias)	Quote: "Interested individuals were […] given a brief explanation of the study; […]. Ten participants […], upon learning of assignment to the SOG (Screening only group) refused to participate, […]." Comment: Blinding of participants and personnel was not feasible due to the nature of the intervention. The outcomes in this trial are likely to be influenced by this lack of blinding as they are mainly behavioural outcomes.	High risk
Blinding of outcome assessment (detection bias) (subjective and behavioural outcomes)	Quote: "All lifestyle risk factors were self-reported and were not corroborated by direct observation." Comment: As participants were not blinded and the assessment of this group of outcomes is likely to be influenced by a lack of blinding, the risk of bias is high.	High risk
Blinding of outcome assessment (detection bias) (objective outcomes)	Comment: No information given regarding the blinding of outcome assessment and thus, the risk of bias remains unclear.	Unclear risk
Incomplete outcome data (attrition bias)	Quote: "There was a loss to follow-up of 30.5% in the SEG (Screening plus Education Group) and 17.5% in the SOC (Screening only) over the 2 years of study." Quote: "Given the overall attrition rate of 26.2%, potentially bias was introduced due to this loss to follow-up." Comment: The risk of bias is high due to the high proportions of missing data in both groups and also due to the imbalance in numbers for missing data across intervention groups.	High risk
Selective reporting (reporting bias)	Comment: All outcomes pre-specified in the methods section of the publication have been reported in the results section. However, some findings were not evaluable due to contradictory information provided in the text and the figures of the publication.	High risk
Other bias	Quote: "There is a possibility that, because the intervention and comparis on participants lived in the same CCRC, there was a diffusion of the osteoporosis education shared in the class to members of the comparison group. In this way, the effects of the education offered to those randomised to the intervention group (SEG) may have been diluted. However, the 2 CCRCs used for this study each have populations in excess of 1800 residents. The study sample at Site A represented approximately 13% of the resident population and approximately 5% of the population at Site B. Therefore, this effect, if it did occur, may have been negligible." Comment: As the argumentation of the authors seems reasonable, the risk of bias due to this possible diffusion is thought to be low.	Low risk
Gardner et al. [26]		
Domain	Support for judgement	Author's judgement
Random sequence generation (selection bias)	Quote: "The patients were randomly enrolled into two groups by means of sealed envelopes, which were divided equally into 'control group' and 'study group' designations."	Low risk
Allocation concealment (selection bias)	Comment: The description of concealment is not described in sufficient detail as it remains unclear whether the envelopes were sequentially numbered and opaque.	Unclear risk
Blinding of participants and personnel (performance bias)	Comment: Blinding of participants and personnel is not feasible due to the nature of the intervention. The outcomes are at risk to be influenced by this lack of blinding.	High risk
Blinding of outcome assessment (detection bias) (subjective and behavioural outcomes)	This trial did not assess any subjective or behavioural outcomes.	–
Blinding of outcome assessment (detection bias) (objective outcomes)	Quote: "We relied on the patient's self-report by telephone, of whether dual-energy x-ray absorptiometry scan had been performed or medication had been prescribed. There was no verification that an interaction or lack thereof actually occurred. While these are generally considered to be relatively major events that a patient is likely to recall, this is still a potential source of error."	High risk
Incomplete outcome data (attrition bias)	Quote: Forty patients were randomised to the control group. Four of them died before the six-month follow-up call and were excluded from the analysis, and five patients were lost to follow-up and were considered not to have been treated for osteoporosis. […] Forty patients were	Low risk

Table 8 (continued)

	randomised to the study group. Four of them died within six months after the surgery and were excluded, and two patients were lost to follow-up and were considered not to have been treated for osteoporosis." Comment: Data is missing in both groups and the exclusions (due to mortality) are justifiable. The reasons for missing outcome data are similar across the study groups and the method used to deal with missing data seems appropriate. Thus the risk of bias is low.	
Selective reporting (reporting bias)	Comment: All outcomes pre-specified in the methods section of the publication have been reported in the pre-specified way in the results section; non-significant results have been reported in the same manner as significant results.	Low risk
Other bias	Comment: No other sources of bias could be identified.	Low risk
Guilera et al. [35]		
Domain	Support for judgement	Author's judgement
Random sequence generation (selection bias)	Quote: "we applied cluster randomization per practice. […] Practises were randomised for educational intervention […] or control group […]." Comment: Insufficient information provided about the sequence generation process to permit a judgement of low or high risk of bias.	unclear risk
Allocation concealment (selection bias)	Comment: Insufficient information to permit judgement of low or high risk, as the method used for allocation concealment is not described.	Unclear risk
Blinding of participants and personnel (performance bias)	Quote: "Moreover, despite the use of cluster randomization per practice, the investigators were not blind to the intervention and could subsequently have modified and improved their usual care." Comment: Patients are also unlikely to be blinded as blinding is not feasible due to the nature of the intervention. As the outcomes are subjective or behavioural outcomes, they are likely to be influenced by lack of blinding.	High risk
Blinding of outcome assessment (detection bias) (subjective and behavioural outcomes)	Quote: "Adherence was assessed by the Morisky-Green test. This is a self-reported measure that, although valid, has been shown to overestimate patient adherence to therapy." Comment: As patients were not blinded, a high risk of bias exists for all outcomes of this trial (adherence and quality of life).	High risk
Blinding of outcome assessment (detection bias) (objective outcomes)	This trial did not assess any objective outcomes.	–
Incomplete outcome data (attrition bias)	Comment: 97 patients (26.5%) in the IG and 120 patients (31.67%) in the CG did not complete the study. Quote: "A high proportion of patients was lost to follow-up, and, if they had lower compliance and worse HRQOL, our results may overestimate both outcomes." Comment: Although the missing outcome data is balanced in numbers across the two groups, the attrition rate is very high and thus the risk of bias is high.	High risk
Selective reporting (reporting bias)	Comment: All outcomes pre-specified in the methods section of the publication have been reported in the pre-specified way in the results section; non-significant results have been reported in the same manner as significant results.	Low risk
Other bias	Comment: In this trial, cluster-randomisation was used, which can lead to several biases. The individual participants were recruited after the clusters have been randomised and thus, a recruitment bias may occur. Additionally, the results were analysed as though the unit of allocation had been the individual participants. This can lead to a so called "unit-of-analysis error", which was not addressed in the analyses. Quote: "Finally, analyses were not adjusted according to the intra-cluster correlation coefficient (ICC), and the effect size of the intervention may have been overestimated."	High risk
Nielsen et al. [36], [37] (registered at ClinicalTrials.gov: ID: NCT00414154)		
Domain	Support for judgement	Author's judgement
Random sequence generation (selection bias)	Quote (publication from 2008): "300 patients […] were randomised in blocks of eight to either intervention group […] or control group." Comment: The process of selecting blocks was not specified (e.g. using a random number table) and thus the information provided is insufficient to permit a judgement of low or high risk of bias.	unclear risk
Allocation concealment (selection bias)	Comment: Insufficient information to permit judgement of low or high risk, as the allocation concealment method is not described.	Unclear risk
Blinding of participants and personnel (performance bias)	Quote (trial register): "Masking: Open label" Comment: The outcomes in this trial are likely to be influenced by the lack of blinding as they are mainly behavioural outcomes.	High risk

Table 8 (continued)

Blinding of outcome assessment (detection bias) (subjective and behavioural outcomes)	Quote (publication from 2010): "All data were self-reported and may therefore be overestimated, if participants in the school group wished to please the teaching staff."	High risk
Blinding of outcome assessment (detection bias) (objective outcomes)	Quote (publication from 2008): "The participants' knowledge […] was tested using a validated, self-administrated questionnaire, […]." Comment: It remains unclear whether the assessor who analysed the questionnaires returned by the participants was blinded.	Unclear risk
Incomplete outcome data (attrition bias)	Quote (publication from 2008): "141 patients […] and 128 patients […] in the school group and the control group, respectively, returned the questionnaire at inclusion and after 3 months." (Note: 150 patients were initially randomised to each group) Quote (publication from 2008): "the dropout rate seemed to be higher in the control group, and this might, in theory, skew the results; however, the dropout rates did not differ significantly between groups." Comment: In the publication from 2010 the dropout rates were reported as follows: At the 3-months follow up, 146 patients in the IG and 137 in the CG returned the questionnaire. At the 24-months follow-up, the number of patients was 136 in the IG and 130 in the CG. This information does not match the information provided in the report published in 2008. Depending on which numbers are used to calculate the dropout rates, the rate is 3–9% for the IG and 9–15% for the CG. These rates are acceptable and the differences between the groups are not significant, thus the risk of bias is low.	Low risk
Selective reporting (reporting bias)	Comment: According to the trial register, four other secondary outcomes (namely quality of life, physical activity, daily dietary calcium intake and falls in- and outdoor) were supposed to be assessed in this trial. No information is given regarding these outcomes in the two published reports.	High risk
Other bias	Comment: A potential source of bias is the use of blocked randomisation in unblinded trials. This combination can create a risk of selection bias, especially if the block size is fixed and smaller than ten. It is then possible to predict future assignments. Quote (publication from 2010): "The adherence questionnaire has not been validated […]." Comment: Using a non-validated questionnaire can affect internal validity and introduce a risk of bias. Overall, the risk of bias is high, because of these two limitations.	High risk
Pekkarinen et al. [38] (registered at ClinicalTrials.gov: NCT00589615)		
Domain	Support for judgement	Author's judgement
Random sequence generation (selection bias)	Quote: "The coordinator, not in contact with the intervention, carried out a simple randomisation and allocated potential participants into the IG and the CG." Quote: "Our randomisation system may be criticised. We randomly collected two pools of potentially eligible subjects from the Population Central Register and offered the intervention to one and the follow-up to another." Comment: Usually a pool of eligible patients is selected and then a randomisation system (e.g. using a computer generated list of random numbers) is applied to allocate eligible patients into the study groups after the participants gave informed consent. As this was not done in this study, the selection process may be at risk of bias.	High risk
Allocation concealment (selection bias)	Comment: Potential participants knew which study group they have been allocated to before they decided on their participation. Thus, the allocation was not concealed and this knowledge might have influenced the potential participant's decision whether or not to participate.	High risk
Blinding of participants and personnel (performance bias)	Quote (trial register): "Masking: Open label" Comment: The outcomes are likely to be influenced by this lack of blinding as they are mainly behavioural outcomes.	High risk
Blinding of outcome assessment (detection bias) (subjective and behavioural outcomes)	Quote: "We had to rely on self-report questionnaires to ask for diseases and medications, which may be another potential limitation." Comment: Data on lifestyle factors regarding outcomes such as physical activity, smoking status, medication use etc. were also collected via self-administered questionnaires and at high risk for bias as patients were not blinded.	High risk
Blinding of outcome assessment (detection bias) (objective outcomes)	Quote: "We identified hip fractures […] from the National Hospital Discharge Register, […]." Quote: "Mortality data […] were obtained from the National Cause of Death Register, Statistics Finland." Comment: Although no information is provided about the blinding of the outcome assessment, even in the case of unblinded assessors, the lack of blinding is unlikely to influence the outcome measurement.	Low risk

Table 8 (continued)

Incomplete outcome data (attrition bias)	Quote: "Of the 1004 women in the IG, 716 (71%) were completers and 289 (29%) non-completers; the respective numbers for the 1174 women in the CG were 733 (62%) and 441 (38%), $P = 0.56$. Of the non-completers in the IG, 89 died and 200 withdrew; the respective numbers for the non-completers in the CG were 125 and 316." Quote: "Yet, due to the reducing number of participants who returned questionnaires during follow up, we must be cautious when analysing the changes in lifestyle."	High risk
Selective reporting (reporting bias)	Comment: No outcomes provided in the trial register. All outcomes pre-specified in the methods section of the publication have been reported in the pre-specified way in the results section; non-significant results have been reported in the same manner as significant results; all results are reported in a very detailed way.	Low risk
Other bias	Comment: No other sources of bias could be identified	Low risk
Plawecki et al. [27]		
Domain	Support for judgement	Author's judgement
Random sequence generation (selection bias)	Quote: "Randomization was to either treatment ($n = 35$) or control group ($n = 34$), blocked on gender and availability." Comment: Insufficient information provided about the sequence generation process to permit a judgement of low or high risk of bias.	Unclear risk
Allocation concealment (selection bias)	Comment: Insufficient information to permit judgement of low or high risk, as the method used for allocation concealment is not described.	Unclear risk
Blinding of participants and personnel (performance bias)	Quote: "It is difficult to interpret these findings, but being enrolled in a study may have a bias on the participants. […] The only way to blind for this potential bias would be to enrol participants in a larger study in which health, and bone health in particular, was nested within a different topical framework." Comment: Thus, blinding of participants and personnel was not feasible due to the nature of the intervention and the outcomes in this trial are likely to be influenced by the lack of blinding as they are all behavioural outcomes.	High risk
Blinding of outcome assessment (detection bias) (subjective and behavioural outcomes)	Comment: All outcomes are measured by patient's self-report and thus at high risk of bias as participants were not blinded.	High risk
Blinding of outcome assessment (detection bias) (objective outcomes)	This trial did not assess any objective outcomes.	–
Incomplete outcome data (attrition bias)	Comment: In total, 7 participants (10%) did not finish the program, 4 in the IG and 3 in the CG. Thus, the overall attrition rate is reasonably low and the missing outcome data is balanced in numbers across the two groups.	Low risk
Selective reporting (reporting bias)	Comment: All outcomes pre-specified in the methods section of the publication have been reported in the pre-specified way in the results section; non-significant results have been reported in the same manner as significant results.	Low risk
Other bias	Comment: No other sources of bias could be identified.	Low risk
Rolnick et al. [28]		
Domain	Support for judgement	Author's judgement
Random sequence generation (selection bias)	Quote: "Subjects meeting eligibility criteria ($n = 508$) were randomly assigned to one of two groups." Comment: Insufficient information provided about the sequence generation process to permit a judgement of low or high risk of bias. Additionally, randomisation was only performed for the two intervention groups. Control subjects were selected from the same managed care organisation and matched to each subject of one of the intervention groups. This is a potential source of bias and hence, the risk of bias is high.	High risk
Allocation concealment (selection bias)	Comment: No information provided regarding the allocation concealment of the two intervention groups. Additionally, participants and study coordinators knew that the first cohort would receive an intervention and the second cohort would be the control group. Thus, the risk of bias is high.	High risk
Blinding of participants and personnel (performance bias)	Comment: Blinding of participants and personnel is not feasible due to the nature of the intervention. The outcomes are likely to be influenced by this lack of blinding as they are mainly behavioural outcomes.	High risk
Blinding of outcome assessment (detection bias) (subjective and behavioural outcomes)	Quote: "All subjects were mailed a follow-up survey." Comment: The risk of bias is high as the outcomes are self-reported by patients who are not blinded and behavioural outcomes are likely to be influenced by this lack of blinding.	High risk

Table 8 (continued)

Blinding of outcome assessment (detection bias) (objective outcomes)	Quote: "Prescription data from computerized pharmacy records were obtained for all subjects for the 6 months after the educational session to confirm initiation of pharmaceutical treatment for osteoporosis. Computerized records were also checked for any BMD procedures during the 6 months after intervention." Comment: In this case, lack of blinding is unlikely to influence the outcome measurement.	Low risk
Incomplete outcome data (attrition bias)	Quote: "Many women expressed disappointment at being assigned to the education only group at the screening telephone call. […] Those assigned to the education only arm of the study were significantly more likely to not attend the education session than those assigned to education with BMD (124 women or 29% versus 22 women or 10%, p = <0.001). […] Subjects from the education plus BMD group were more likely to respond to the follow-up survey than subjects from the education only group (94% vs. 87%, $p < 0.05$)." Quote: "Of the subjects who were eligible and randomly assigned to the study ($n = 654$), 146 did not attend the educational session, leaving a final sample size of 508. […] About 22% of the intervention subjects that were randomly assigned to an intervention dropped out of the study. If the most interested and knowledgeable women stayed in, it could account for intervention versus control group differences."	High risk
Selective reporting (reporting bias)	Comment: All outcomes pre-specified in the methods section of the publication have been reported in the pre-specified way in the results section; non-significant results have been reported in the same manner as significant results.	Low risk
Other bias	Comment: No other sources of bias could be identified.	Low risk
Schousboe et al. [29]		
Domain	Support for judgement	Author's judgement
Random sequence generation (selection bias)	Quote: "A statistician […] otherwise uninvolved with the study used a random number generator to generate three sets of assignment codes, one for each strata of BMD."	Low risk
Allocation concealment (selection bias)	Quote: "Each assignment was stored in an opaque sealed white envelope, which was not opened by the nurse educator until informed consent to participate had been signed and BMD ascertained."	Low risk
Blinding of participants and personnel (performance bias)	Comment: Blinding of participants and personnel is not feasible due to the nature of the intervention. The outcomes are likely to be influenced by this lack of blinding as they are mainly behavioural outcomes.	High risk
Blinding of outcome assessment (detection bias) (subjective and behavioural outcomes)	Quote: "Interviewers were not blinded to the participants' group assignment […]. To limit the influence of unblinded interviewers' bias, interviewers were instructed to ask the questions specifically as written in the questionnaire script." Quote: "Medication adherence is overestimated by self-report […]." Quote: "The 12-month assessments were unblinded; hence, interviewer bias could have influenced respondents' answers." Comment: Although the authors said the influence of unblinded interviewers' bias was limited by instructions to the interviewers to ask questions specifically as written in the script, this could not be monitored and the risk of bias remains high, also due to the fact that the outcomes are self-reported by the patients who were unblinded.	High risk
Blinding of outcome assessment (detection bias) (objective outcomes)	Comment: The data for the objective outcome (namely initiation of pharmacological therapy) was not obtained from medical records, but through patients' report. As patients were not blinded, the risk of bias is high (for example if patients gave false information to please the study staff).	High risk
Incomplete outcome data (attrition bias)	Quote: "Of the 310 participants who enrolled, 158 were assigned to the nurse education group and 152 to the usual care group. A total of 287 patients completed the study, 147 from the nurse education group and 140 from the usual care group." Comment: Thus, 7% in the nurse education group and 8% in the usual care group did not complete the study. This is a low attrition rate and the missing outcome data is balanced in numbers across the two groups and thus, the risk of bias is low.	Low risk
Selective reporting (reporting bias)	Comment: All outcomes pre-specified in the methods section of the publication have been reported in the pre-specified way in the results section; non-significant results have been reported in the same manner as significant results.	Low risk
Other bias	Quote: "Participants then had bone densitometry of the lumbar spine and hip on a Hologic QDR-4500sl dual-energy x-ray absorptiometer […],	High risk

Table 8 (continued)

	and were divided into three strata defined according to BMD score" Comment: As the BMD measurement was conducted before randomisation to allocate participants to one of the three strata, and patients are likely to know their results of the BMD test, this knowledge might have an impact on their health-directed behaviour and thus it could enhance or diminish the effect of the following randomised intervention.	
Tüzün et al. [33]		
Domain	Support for judgement	Author's judgement
Random sequence generation (selection bias)	Quote: "Randomization was performed centrally by means of 20-patient block design." Comment: It is very unlikely that the sequence generation process involves any systematic, non-random approaches such as sequence generations based on dates of birth or admission dates when randomisation is performed centrally. Thus the risk of bias is low.	Low risk
Allocation concealment (selection bias)	Comment: By using central randomisation, investigators cannot foresee the group assignment and thus the risk of bias is low.	Low risk
Blinding of participants and personnel (performance bias)	Comment: Blinding of participants and personnel is not feasible due to the nature of the intervention. The outcomes are likely to be influenced by this lack of blinding as they are mainly subjective or behavioural outcomes.	High risk
Blinding of outcome assessment (detection bias) (subjective and behavioural outcomes)	Quote: "The primary evaluation criteria were treatment compliance and persistency based on the information given to the investigator by the patient." Quote: "Due to the observational nature of the study no strict monitoring devices were used to determine the compliance of the patient. Instead we relied on voluntary patient information to determine if the medications were taken on a timely manner, at the recommended dosages, per physicians' instructions. Some patients may feel embarrassed to admit that they missed some doses or did not follow instructions."	High risk
Blinding of outcome assessment (detection bias) (objective outcomes)	Comment: No information given regarding the blinding of outcome assessment and thus, the risk of remains unclear.	Unclear risk
Incomplete outcome data (attrition bias)	Quote: "A total of 448 female patients […] were included in the study. […] 305 patients (155 from the AT group and 150 in the PT group) completed the study." Comment: Thus, 143 participants (32%) did not complete the study. This is a fairly high proportion and if they had a lower or higher compliance than the patients that did not drop out, the results may be over- or underestimated.	High risk
Selective reporting (reporting bias)	Comment: All outcomes pre-specified in the methods section of the publication have been reported in the pre-specified way in the results section; non-significant results have been reported in the same manner as significant results.	Low risk
Other bias	Comment: A potential source of bias is the use of blocked randomisation in unblinded trials. This combination can create a risk of selection bias, especially if the block size is fixed and smaller than ten. In this case, the risk of bias remains low though, as the randomisation was performed centrally and it can be assumed that the investigators were blind to the size of blocks. Additionally, this issue is unlikely to occur when the block size is bigger than ten. No other sources of bias could be identified	Low risk
Yuksel et al. [30]; [31]; [52] (registered at ISRCTN: ID: ISRCTN54746861)		
Domain	Support for judgement	Author's judgement
Random sequence generation (selection bias)	Quote: (publication from 2010): "Patients […] were randomised via a secure internet randomization service (using a sequence stratified by site with a block size of 4) to intervention or control."	Low risk
Allocation concealment (selection bias)	Comment: By using a central allocation such as a web-based allocation, investigators cannot foresee the assignment and thus the risk of bias is low.	Low risk
Blinding of participants and personnel (performance bias)	Quote (publication from 2010): "[…] but given the nature of the study all patients were aware of taking part in an osteoporosis quality improvement study." Comment: Due to the nature of the study it is also unlikely that personnel were blinded. Additionally, the outcomes are likely to be influenced by this lack of blinding as they are mainly subjective or behavioural outcomes.	High risk
Blinding of outcome assessment (detection bias) (subjective and behavioural outcomes)	Quote (publication from 2010): "All outcomes were ascertained without knowledge of allocation status, but given the nature of the study all patients were aware of taking part in an osteoporosis quality improvement study." Comment: Thus, the risk of bias remains high for outcomes such as quality of life or calcium and vitamin D intake.	High risk

Table 8 (continued)

Blinding of outcome assessment (detection bias) (objective outcomes)	Quote (publication from 2010): "This was a randomised controlled trial with blinded ascertainment of outcomes. […] All outcomes were ascertained without knowledge of allocation status, […]." Quote (publication from 2010): "Endpoints were measured by patient self-report and confirmed by receiving a copy of the BMD measurement from the primary care physician and a copy of the prescription from the dispensing pharmacy."	Low risk
Incomplete outcome data (attrition bias)	Quote (publication from 2010): "All analyses were according to the intention-to-treat principle. […] Overall, 262 patients were randomised […]. After allocation, 26 (20%) patients in the intervention group and 23 (17%) controls either withdrew or were lost to follow-up. All 202 patients were included in the analyses." Quote (publication from 2010): "[…] with nearly half of the withdrawals occurring before the intervention was actually delivered." Comment: Missing outcome data is balanced in numbers across the two groups with similar reasons for missing data, and appropriate methods (intention-to-treat) have been used to impute missing data.	Low risk
Selective reporting (reporting bias)	Comment: All outcomes pre-specified in the trial register and the study protocol have been reported in the pre-specified way in the published report; non-significant results have been reported in the same manner as significant results.	Low risk
Other bias	Comment: A potential source of bias is the use of blocked randomisation in unblinded trials. This combination can create a risk of selection bias, especially if the block size is fixed. In this case, the risk of bias remains low though, as the randomisation was performed centrally, and from the information provided in the publication it is understood that the investigators were blind to the block size and did not get to know the group allocation after the assignment either No other sources of bias could be identified.	Low risk

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