Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis (Review)

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[Intervention Review]

Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis

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ABSTRACT

Background

Vitamin D and related compounds have been used to prevent osteoporotic fractures in older people.

Objectives

To determine the effects of vitamin D or related compounds, with or without calcium, for preventing fractures in older people.

Search strategy

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register, the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2007, Issue 3), MEDLINE, EMBASE, CINAHL, and reference lists of articles. Most recent search: October 2007.

Selection criteria

Randomised or quasi-randomised trials comparing vitamin D or related compounds, alone or with calcium, against placebo, no intervention, or calcium alone, reporting fracture outcomes in older people.

Data collection and analysis

Two authors independently assessed trial quality, and extracted data. Data were pooled, where admissible, using the fixed-effect model, or random-effects model if heterogeneity between studies appeared high.

Main results

Forty-five trials were included.

Vitamin D alone appears unlikely to be effective in preventing hip fracture (nine trials, 24,749 participants, RR 1.15, 95% CI 0.99 to 1.33), vertebral fracture (five trials, 9138 participants, RR 0.90, 95% CI 0.42 to 1.92) or any new fracture (10 trials, 25,016 participants, RR 1.01, 95% CI 0.93 to 1.09).

Vitamin D with calcium reduces hip fractures (eight trials, 46,658 participants, RR 0.84, 95% CI 0.73 to 0.96). Although subgroup analysis by residential status showed a significant reduction in hip fractures in people in institutional care, the difference between this and the community-dwelling subgroup was not significant (P = 0.15).

Overall hypercalcaemia is significantly more common in people receiving vitamin D or an analogue, with or without calcium (18 trials, 11,346 participants, RR 2.35, 95% CI 1.59 to 3.47); this is especially true of calcitriol (four trials, 988 participants, RR 4.41, 95% CI 2.14 to 9.09). There is a modest increase in gastrointestinal symptoms (11 trials, 47,042 participants, RR 1.04, 95% CI 1.00 to 1.08, P = 0.04) and a small but significant increase in renal disease (11 trials, 46,537 participants, RR 1.16, 95% CI 1.02 to 1.33).

Authors' conclusions

Frail older people confined to institutions may sustain fewer hip fractures if given vitamin D with calcium. Vitamin D alone is unlikely to prevent fracture. Overall there is a small but significant increase in gastrointestinal symptoms and renal disease associated with vitamin D or its analogues. Calcitriol is associated with an increased incidence of hypercalcaemia.

PLAIN LANGUAGE SUMMARY

Vitamin D and related vitamin D compounds for preventing fractures resulting from osteoporosis in older people.

Vitamin D is necessary for building bone. Older people often have low vitamin D levels through lack of exposure to sunlight and low dietary intake. Therefore, it has been suggested that taking additional vitamin D supplements may help to reduce the risk of hip and other fractures, which are very common in older people.

This review included 45 trials with 84,585 participants. The review found that taking vitamin D alone is unlikely to prevent fracture. Vitamin D taken with additional calcium supplements does appear to reduce risk of hip fractures in people living in institutional care. Although the risk of harmful effects from vitamin D and calcium is small, some people, particularly with kidney stones, kidney disease or high blood calcium, should seek medical advice before taking these supplements.

Risk of kidney stones was so small that not a single one appears to have been reported in the 84,000 participants. (result of searching this report for KIDNEY)

BACKGROUND

Description of the condition

Involutional and post menopausal osteoporosis, a gradual loss of bone mass, is a complex chronic, multifactorial process and, apparently, an accompaniment to normal ageing in all mammalian species. It derives its public health importance from its association with the development of characteristic fractures late in life, and from the current ageing of the population, particularly in industrialised societies. Both sexes are affected, but the main burden of disease is in women. In the USA the lifetime risk of hip fracture, the most disabling osteoporotic fracture, is at least 17.5% in white women and 6.0% in men (Melton 2000). In the UK the lifetime risk of hip fracture for a women aged 50 years is estimated at 11.4%, and for men aged 50 years 3.1% (Van Staa 2001). In the USA for clinically evident vertebral fractures and distal forearm fractures the lifetime risk after the age of 50 years for women is 15.6% and 16.0%, and men 5.0% and 2.5%, respectively (Melton 2000). In the UK the lifetime risk for a woman aged 50 years for a distal forearm fracture is 16.6% and for a clinically evident vertebral fracture 3.1%; the respective figures for a man aged 50 years are 2.9% and 1.2% (Van Staa 2001). A high proportion of vertebral fractures do not come to clinical attention, and may not cause symptoms but undiagnosed vertebral fractures may be associated with increased back pain and functional limitation (Nevitt 1998). Criteria used to define vertebral fractures in radiographs

differ, but studies suggest that one third to half of women over the age of 75 years have vertebral fractures in Europe and North America (Cummings 2002).

Description of the intervention

The primary goal of the various interventions, such as vitamin D, which have been proposed for osteoporosis is the prevention of fractures. While slowing progressive bone loss plausibly reduces fracture rates, other factors, particularly fall rate in older people, are clearly involved (Cummings 1995). Effective strategies may require the institution of prophylactic measures many years before fractures are likely to occur. The conduct of randomised controlled trials of effectiveness in this context is difficult. Financial, academic and commercial pressures have favoured the selection of short term intermediate outcomes, such as changes in bone mineral density, as evidence of efficacy, but the effectiveness of interventions can best be measured using fracture outcomes.

How the intervention might work

Vitamin D is one of a number of agents with known biologic effects on mineral homeostasis, acting mainly upon the intestine, kidneys and bone. Intestinal calcium absorption is stimulated, and bone mass protected (Norman 1993) although the benefit is largely lost within two years of supplement discontinuation (Dawson-Hughes 2000). Vitamin D is mostly derived from ultraviolet sunlight exposure of the skin. Although there are a few dietary sources, such as oily fish, these contribute relatively little vitamin D (known as D3, cholecalciferol), except in people who consume oily fish several times a week. Synthetic vitamin D (known as D2, ergocalciferol) is frequently the form provided in supplements, and this may not be equivalent to vitamin D3 (Houghton 2006).

Administration of vitamin D, and particularly its derivatives (analogues) (*see* Table 1), may carry a risk of hypercalcaemia and hypercalciuria (high levels of calcium in the blood and urine, respectively). Adequate calcium intake may also protect bone mass (Cumming 1990), but calcium supplements may provoke gastrointestinal symptoms. There is a winter decline in circulating vitamin D concentrations in older people living at high latitudes may be correctable by a single injection of cholecalciferol (Khaw 1994). However the bioavailability of intramuscular vitamin D is variable and may be very poor, and high dose intermittent oral supplementation may be more reliable (Romagnoli 2008). The rates of hip fracture vary annually with a winter peak in both Northern and Southern hemispheres (Jacobsen 1990; Lau 1995). Inadequate vitamin D levels have been demonstrated in patients with osteoporosis (Lips 2006), including hip fracture in many countries, although low levels may be influenced by the fracture itself (Boonen 1996; LeBoff 1999; Pieper 2007).

Table 1. Vitamin D nomenclature, synonyms and abbreviations

Vitamin D	Synonyms	Graph abbreviations
Vitamin D: two forms are vitamin D2 and vitamin D3		
Vitamin D2	Ergocalciferol	D2
Vitamin D3	Cholecalciferol	D3
25-hydroxy vitamin D: vitamin D with one hydroxyl group added equivalent to liver activation.	Calcidiol	25(OH)D
1-alpha-hydroxy vitamin D3*: vitamin D with one hydroxyl group added equivalent to renal activation.	Alfacalcidol	1-alpha(OH)D3
1,25 dihydroxy vitamin D3*: vitamin D with two hydroxyl groups added equivalent to both liver and renal activation.	Calcitriol	1,25(OH)2D3

* denotes analogues/derivatives
Ca: abbreviation for calcium in graphs

Why it is important to do this review

Vitamin D itself is inexpensive and an attractive candidate agent for use in public health interventions, particularly if it can be given intermittently in high dosage. A randomised trial widely quoted as supporting the effectiveness of vitamin D (Chapuy 1992) evaluated co-administration of daily oral vitamin D3 and calcium supplements. Calcium co-supplementation means that daily tablets are required, which may influence compliance, and calcium may be associated with gastrointestinal side-effects (RECORD 2005). Compared with vitamin D, the vitamin D analogues calcitriol (1,25 dihydroxy vitamin D3) and alfacalcidol (1-alpha-hydroxy vitamin D3) are more expensive. As costs are critical in the selection of preventive programmes, systematic review of current evidence for effectiveness of vitamin D analogues, with and without calcium, in fracture prevention in older people should inform practice and research. This review is an update of Avenell 2005.

OBJECTIVES

To determine the efficacy of supplementation with vitamin D or a vitamin D related compound in the prevention of hip, non-vertebral, vertebral or any new fracture. To determine the effect of supplementation on the incidence of hypercalcaemia, gastrointestinal effects, renal disease (calculi or insufficiency) and deaths.

The following hypotheses were tested:

The use of supplementation with vitamin D or a vitamin D related compound, either alone, or in combination with calcium, reduces the incidence of hip, non-vertebral, vertebral or any new fracture in older people.

We also planned to explore two secondary hypotheses, both raised on the basis of previously established associations through subgroup analysis. These were:

The use of supplementation with vitamin D or a vitamin D related compound, either alone, or in combination with calcium, reduces the incidence of hip, non-vertebral, vertebral or any new fracture in older people with a history of previous osteoporotic fracture.

The use of supplementation with vitamin D or a vitamin D related compound, either alone, or in combination with calcium, reduces the incidence of hip, non-vertebral, vertebral or any new fracture in a population of old, frail people (defined in this review by residence in institutions e.g. nursing homes or residential care home).

METHODS

Criteria for considering studies for this review

Types of studies

Any randomised trial or quasi-randomised (method of allocating participants to a treatment which is not strictly random e.g. by date of birth, hospital record number, alternation) trial meeting the criteria for participants, interventions or outcomes listed below.

Types of participants

Men over 65 years of age and post-menopausal women. We included trials whose participants had neurologic disease impairing mobility (for example, after stroke or in Parkinson's disease) but excluded studies focussed on participants on corticosteroid therapy, which is the subject of another Cochrane review (Homik 1998).

Types of interventions

Administration of vitamin D or a vitamin D related compound, either alone or in combination with calcium supplementation compared with a placebo, no intervention, or the administration of calcium supplements (*see* Table 1 for details of nomenclature of interventions). Interventions incorporating treatments other than vitamin D and calcium were not considered, e.g. vitamin D and hormone replacement therapy (HRT) compared with HRT alone. In defining a comparison, advice on dietary modification to increase calcium intake was not considered as supplementation.

Types of outcome measures

Primary outcomes

- Hip fracture

Secondary outcomes

- Any non-vertebral fracture. Non-vertebral fractures were defined as all fractures except those of the vertebrae, but including hip fractures.
- Vertebral fracture (two outcomes were sought: clinical fracture events, and new vertebral deformity identified by radiological morphometry or semi-quantitative reading by a radiologist, using routine radiographs, according to a defined experimental protocol. Any of these described methods appear to provide a valid approach to defining vertebral deformity (Black 1995)).
- Any new fracture (i.e. fractures not covered by the previous three categories. Any new fracture includes all fractures from studies which do not report results by fracture location).
- Adverse effects (hypercalcaemia, renal disease, gastrointestinal symptoms and death).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (to September 2007), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2007, Issue 3, Wiley InterScience), MEDLINE (1966 to August week 4 2007, Ovid Web), EMBASE (1980 to week 35 2007, Ovid Web), CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1982 to August week 4 2007, Ovid Web), LILACS (Latin American and Caribbean Health Sciences) (searched to September 2000), CABNAR (Commonwealth Agricultural Bureau Nutrition Abstracts and Reviews) (1984 to July 2007), BIOSIS (1985 to September 6 2007), HealthSTAR (1975 to Mar 2002), and Current Contents (to 1996).

In MEDLINE (OVID Web) we combined subject specific terms with the Cochrane optimal trial search strategy (Dickersin 1994), and modified this strategy for use in EMBASE (*see* Appendix 1).

We identified ongoing studies by searching all registers in Current Controlled Trials (September 2007).

Searching other resources

We also checked reference lists of articles and contacted active researchers in the field. We handsearched abstracts published in the Journal of Bone and Mineral Research (volume 1 part 1 to September 2007, volume 22 part 9), Bone (volume 22 part 1 to September 2007, volume 41 part 3), Calcified Tissue International (volume 62 part 1 to September 2007, volume 81 part 3), and Osteoporosis International (volume 8 part 1 to October 2007, volume 18 part 10).

No restrictions were placed on language of publication.

Data collection and analysis

Selection of studies

The citations of potentially eligible studies were entered into the Review Manager (RevMan) software. Copies of all references were retrieved and sorted on the basis of the described criteria into included and excluded trials, each being reviewed by at least two authors. For each included trial, assessment of methodological quality and data extraction were carried out as detailed below. Qualitative details and published data describing study population, interventions, and outcomes were entered.

Quality assessment

Methodological quality was assessed independently by two authors using a pre-derived scoring schedule and a coding instruction manual. The assessment protocol scored each item between 0 and 2 (*see* Table 2 for the quality assessment items and possible scores). Pre-allocation disclosure of assignment was also coded A, B, or C according to the Cochrane Handbook (Higgins 2006a). Disagreement between raters was adjudicated by a third rater.

Table 2. Quality assessment items and possible scores

Items	Scores
Item A Was the assigned treatment adequately concealed prior to allocation?	**Score 2** (and code A) if clearly yes i.e. - Some form of centralised randomisation scheme, such as having to provide participant details by phone to receive treatment group allocation. - A scheme controlled by a pharmacy - In a pharmaceutical study, sequential administration of pre-numbered or coded containers to enrolled participants - An on-site computer system, given that allocations are in a locked unreadable file which can be accessed only after inputting participant details - Assignment envelopes, provided that they are sequentially numbered, sealed, and opaque - Other combinations which appear to provide assurance of adequate concealment **Score 1** (and code B) if unclear i.e. - Assignment envelopes, without description of adequate safeguards - Use of a “list” or “table”

Table 2. Quality assessment items and possible scores (*Continued*)

	- A trial in which the description suggests adequate concealment, but other features are suspicious, for example markedly unequal control and trial groups **Score 0** (and code C) if clearly no i.e. - Alternation - Case record numbers, dates of birth, day of the week, or any other such approach - Any allocation procedure transparent before assignment, such as an open list of random numbers
Item B Were the outcomes of participants who withdrew or were excluded after allocation described and included in an "intention-to-treat" analysis?	**Score 2** if adequate detail of withdrawals and exclusions after randomisation exists, and an intention-to-treat analysis has been, or can be carried out. **Score 1** if number and reasons for withdrawal are mentioned but intention to treat analysis is not possible. **Score 0** if inadequate detail exists to allow the author to check or carry out an intention to treat analysis, or obvious differences with no adjustment.
Item C Were the outcome assessors blind to assignment status?	**Score 2** if blinding of all possible outcome assessors is clearly established. **Score 1** if there is a small or moderate chance of unblinding of assessors, or some but not other assessors who could have been blinded were blinded. **Score 0** if no attempt to blind assessors to the assignment of treatment is reported.
Item D Were the treatment and control group comparable at entry?	**Score 2** if groups are demonstrably comparable in respect of potential confounding factors on inspection of the characteristics on entry (means with some expression of the variation e.g. SD, SE, confidence intervals are required), or differences between groups adjusted for in the analysis (stratification, Mantel-Haenszel technique, logistic regression, multiple regression, multivariate techniques). **Score 1** if confounding appears small: although noted, adjustment has not been made. **Score 0** if description of the treatment groups at baseline, either in text or table, is inadequate to confirm comparability for all plausibly important confounders, or statistically significant differences between the groups are present but no adjustment has been made in the analysis.

Table 2. Quality assessment items and possible scores (*Continued*)

Item E Were the subjects blind to assignment status following allocation?	**Score 2** if effective action has been taken to blind participants to assignment. **Score 1** if in a drug study, or in a study comparing a physical modality with a control, it is unclear whether participants were made aware, or could have become aware, of their assignment prior to measurement of outcomes, or the nature of the trial intervention is such that it is unlikely that they will have effects which allow identification of assignment (e.g. calcium supplements versus placebo). **Score 0** if in a drug study, no treatment rather than a placebo is used, or in a placebo-controlled drug study or in a study of comparable physical modalities, participants became aware of their allocation before outcome assessment and analysis.
Item F Were the providers of care blind to assignment status?	**Score 2** if the study is clearly double or triple blind. **Score 1** if it is unclear whether the treatment providers were blinded to the allocation. **Score 0** if in a placebo controlled drug trial, the providers of care were informed of the treatment allocation before outcome assessment and analysis, or a physical modality was used in one or more arms of the trial.
Item G Were the care programmes, other than the trial options, identical?	**Score 2** if it is clear that the care programmes other than the trial interventions were identical. **Score 1** if differences between the programmes are trivial. **Score 0** if the nature of the care programmes other than the trial interventions is unclear, or there are important differences between the programmes offered, other than the trial interventions.
Item H Were the inclusion and exclusion criteria for entry clearly defined?	**Score 2** if the inclusion and exclusion criteria are clearly defined and indicate that individuals currently exposed to a trial intervention were excluded e.g. vitamin D analogue, hormone replacement therapy. **Score 1** if the inclusion and exclusion criteria as described allow the possibility that individuals may have entered the study currently exposed to a trial intervention, or description of the inclusion and exclusion criteria is inadequate to determine how the sample was made up. **Score 0** if no description, other than age and gender, of inclusion and exclusion criteria was provided.

Table 2. Quality assessment items and possible scores (*Continued*)

Item J Was the ascertainment of fractures and other outcomes active and of clinically appropriate duration?	**Score 2** if some form of concurrent collection of data about fracture e.g. subjects given postcards to mail back etc., with confirmation by interview, and by radiograph if positive, or, for vertebral fracture, routine confirmation by radiograph. **Score 1** if contact was made on a regular basis e.g. six monthly phone call to establish if fracture had occurred or not, with confirmation by radiograph if positive. **Score 0** if fracture was registered as an outcome without confirmation by radiograph.

Data analysis

Data were independently extracted by two authors and, if necessary, adjudicated by a third using a pre-derived data extraction form, and entered into RevMan. For each individual study, we calculated the risk ratio (RR) and 95% confidence intervals (95% CI). For fracture outcomes we used the number or proportion of participants with at least one new fracture at the end of the observation period to calculate the RR and 95% CI. Where it was possible to pool data, the resulting pooled risk ratio was calculated with 95% confidence intervals. Heterogeneity was assessed using the I^2 test (Higgins 2003) in conjunction with the P value from the Chi^2 test and visual inspection. The fixed-effect model was used to pool data unless substantial heterogeneity was present, in which case we used the random-effects model.

Denominators used in calculating the incidence of outcomes for each group in each study were all participants randomised to that group (intention-to-treat analysis), unless that information was unavailable from the published reports or from contact with investigators, in which case we used the denominator in the published report.

In the case of meta-analyses including the cluster randomised trial by Law 2006, adjustments to the number of participants with outcomes and denominators in Law 2006 were made using an intraclass correlation coefficient of 0.026 (derived from Dyer 2004) using methods described in Higgins 2006b. This means that the numbers of participants with outcomes and denominators in meta-analyses including this trial do not reflect the total number actually randomised and having events.

Some trials, such as the RECORD 2005 trial had a factorial design, e.g. calcium and vitamin D supplementation (group 1) and vitamin D supplementation (group 2) compared with calcium supplementation (group 3) and placebo (group 4). In such cases the data in the meta-analyses of fractures refer only to the individual groups of the study, and do not make use of the factorial design to explore the full range of combinations of supplements because of the potential interaction of vitamin D and calcium.

Subgroup analyses were undertaken to explore the two secondary hypotheses described in the 'Objectives' i.e. by history of osteoporotic fracture and by residential status. Statistically significant differences between subgroups were determined by non-overlapping 95% confidence intervals and confirmed by comparing the ratio of the difference in the natural logarithm of the risk ratios and the standard error of the difference in log risk ratios to the standard normal distribution.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Included studies

Forty-five trials were included in this review: 42 were individually randomised controlled trials (RCTs), one was a cluster randomised trial (Law 2006), and two were quasi-randomised (Inkovaara 1983, Meyer 2002) (*see* 'Characteristics of included studies' table for full descriptions).

Settings and sample size

Broadly, the included trials fall into three groups. Fourteen large trials, with between 610 to 36,282 participants, examined the prevention of non-vertebral (including hip) or vertebral fractures. Of these, one trial (Tilyard 1992) compared calcitriol with calcium, and the remainder compared vitamin D2, vitamin D3, or 25-hydroxy vitamin D, with or without co-administration of calcium, against placebo, no treatment, or calcium alone. Law 2006 was also a cluster randomised trial of 223 residential units in 118 homes for older people, which examined three monthly vitamin D2 versus no treatment.

Eight trials with between 150 and 500 participants were conducted in the community. All except one (Dukas 2004) examined the effectiveness of vitamin D alone or with co-administration of calcium. All except Peacock 2000 sought non-vertebral fractures as the main outcome or as an outcome in a falls prevention study (Prince 2008).

The largest group consisted of the remaining 23 smaller trials with fewer than 150 participants in total (or fewer than 150 in the groups relevant to this review as in the case of Bolton-Smith 2007), which contributed data on vitamin D (with or without calcium co-administration), calcitriol or alfacalcidol (1-alpha-hydroxy vitamin D3). Most recruited from referral populations with established osteoporosis or by public advertisement, and were carried out in the setting of institutional referral clinics. In the majority, osteoporosis had been formally diagnosed, and often the presence of one or more deformed vertebrae on an initial radiograph was required for inclusion in the trial. Most participants underwent bone density measurements, or extensive biochemical analyses of blood and urine, or assessment of musculoskeletal function. Radiological vertebral deformity or changes in bone mineral density were the principal outcomes, although other fracture data were sometimes available. Avenell 2004 was a small parallel study to RECORD 2005 with an open design. Three trials from the same author (Sato 1997; Sato 1999a; Sato 1999b) evaluated the effect of alfacalcidol (1-alpha-hydroxy vitamin D3) on the prevention of hip fractures in participants with stroke related hemiplegia or Parkinson's disease.

Excluded studies

Fifty-seven studies were excluded (*see* 'Characteristics of excluded studies' table for details). Most were excluded because the trials did not present fracture data.

Attention is drawn to one particular excluded study, which has been quoted as evidence for effectiveness of single dose vitamin D injection in fracture prevention (Heikinheimo 1992). This study was quasi-randomised (allocation based on month of birth), and there was no attempt at blinding. Only individuals recruited in the northern autumn and winter were included, and there was no placebo. Follow up varied between two to five years but the cumulative analysis of fracture incidence did not include confidence intervals despite the decreasing numbers with longer follow up. Participants who rejected injection were added to the control group. Although considered ineligible for inclusion in this systematic review, this study was important mainly for raising the hypothesis that this relatively inexpensive, practical proposal for fracture prevention should be tested more rigorously.

We also draw attention to an excluded trial, which we had included in the previous version of this review (Avenell 2005) with a note that its result should be treated with caution. Larsen 2004, a cluster randomised study (N = 4 clusters) was not included in our pooled analysis at that time, as the investigators' analysis appeared to be for individually randomised participants. We have now excluded this widely quoted study because it does not meet the inclusion criteria for this review. Participants in each of the three treatment clusters received one or more co-interventions designed to reduce falls (medication review, environmental hazard and health assessment, and osteoporosis/fall prevention leaflets) but the control group received no intervention. No treatment group received vitamin D and calcium alone. Thus, although the investigators state that this was a factorial study, the reports of the design do not appear to fit that description, and the vitamin D and calcium effect cannot be separated from the effects of co-interventions.

Trials of included interventions which do not report fracture data, but do report adverse effects are listed in Table 3 and their details given in the 'Characteristics of excluded studies' table.

Table 3. Selected adverse effects reported in excluded trials

Excluded study ID	Adverse effects
Aloia 2005	Deaths, renal stones, hypercalcaemia
Binkley 2007	Renal insufficiency, hypercalcaemia
Brazier 2005	Deaths, gastrointestinal events, hypercalcaemia
Broe 2007	Deaths

Table 3. Selected adverse effects reported in excluded trials (*Continued*)

Chen 1997	Gastrointestinal events, hypercalcaemia
Corless 1985	Deaths, hypercalcaemia
Daly 2006	Gastrointestinal events
Dawson-Hughes 1991	Renal insufficiency and stones, hypercalcaemia
Doetsch 2004	Deaths
Grady 1991	Deaths, renal insufficiency
Jensen 1982	Hypercalcaemia
Johnson 1980	Hypercalcaemia
Keane 1998	Deaths
Larsen 2004	Deaths
Latham 2003	Deaths
Meier 2004	Deaths
Moschonis 2006	Gastrointestinal events
Ongphiphadhanakul 2000	Hypercalcaemia

Ongoing studies

One ongoing study was identified and details can be found in the 'Characteristics of ongoing studies' table. The Vital D study is examining an annual oral dose of 500,000 IU vitamin D3 in 1500 Australian women aged 70 years or over at high risk of osteoporotic fracture or low vitamin D status.

Studies awaiting classification

A further 13 trials have met, or may meet, the inclusion criteria, but require further information before data can be included (*see* 'Characteristics of studies awaiting classification' table).

New studies found this update

Three studies which were ongoing in the previous version of this review are now included (Law 2006; Lyons 2007; WHI 2006). Five other new trials included are Bischoff 2003, Bolton-Smith 2007, Flicker 2005, Nuti 2006, Prince 2008). One new ongoing trial has been identified (Vital D). Five new trials are awaiting assessment (ALFA 2006; Lappe 2007; Matsumoto 2005; OSTPRE-FPS 2007; Sato 2005). Ten new trials have been excluded (Aguado 2006; Aloia 2005; Binkley 2007; Brazier 2005; Broe 2007; Bunout 2006; Daly 2006; Larsen 2004; Pedrosa 2006; Zhu 2006).

Risk of bias in included studies

Details of the assessment of the methodological quality of each included trial are in Table 4. Reporting of the attributes which made up the methodological evaluation varied widely. Allocation concealment (item A) was adequately reported in 17 (38%) of the included trials, unclear in 26 and not adequate in two. Five trials

did not provide the number of participants allocated to groups at randomisation (Caniggia 1984; Chapuy 2002; Dawson-Hughes 1997; Garay Lillo 1997; Geusens 1986), and one trial provided this information after contacting the author (Flicker 2005). One large trial (Garay Lillo 1997) provided results but very sparse methodological data. Adequate details of withdrawals and exclusions after treatment assignment were provided in 21 trials (47%) (item B). No attempt was reported to blind assessors to treatment assignment in 13 trials (29%) (item C). The intervention and control groups were demonstrably comparable in 26 trials (58%)(Item D). In 62% and 60% of trials respectively, the participants (item E) and/or providers (item F) were blinded to treatment allocation. In the majority of trials (N = 36, 80%) the comparable nature of the care programs, other than the trial interventions, was not reported (item G). The inclusion and exclusion criteria were clearly defined in 36 trials (80%) (item H). Only 18 trials (40%) collected outcome data on fractures as they occurred and confirmed them by interview and radiograph (item J).

Table 4. Quality assessment scores

Study	Item A	Item B	Item C	Item D	Item E	Item F	Item G	Item H	Item J
Aloia 1988	2	1	2	2	2	2	0	2	2
Arthur 1990	1	1	0	1	0	0	0	2	2
Avenell 2004	2	2	0	1	0	0	0	2	1
Bischoff 2003	1	2	2	2	2	2	0	2	0
Bolton-Smith 2007	2	0	2	2	2	2	2	2	0
Caniggia 1984	1	1	0	1	1	1	0	1	2
Chapuy 1992	2	2	1	2	1	1	0	2	1
Chapuy 2002	1	1	1	2	2	2	2	2	1
Dawson-Hughes 1997	1	2	2	0	2	2	1	2	1

Table 4. Quality assessment scores (*Continued*)

Dukas 2004	2	2	0	2	2	2	0	2	0
Ebeling 2001	1	1	2	2	2	2	2	1	1
Falch 1987	1	1	2	1	1	0	0	2	0
Flicker 2005	2	1	2	1	2	2	0	2	2
Gallagher 1989	1	1	2	1	2	2	0	2	2
Gallagher 1990	2	1	2	1	2	2	0	2	2
Gallagher 2001	1	2	2	1	2	2	0	2	1
Garay Lillo 1997	1	0	0	0	0	1	0	2	0
Geusens 1986	1	1	1	0	0	0	0	1	1
Gorai 1999	0	0	0	0	0	0	0	2	2
Harwood 2004	1	2	0	1	0	0	0	2	1
Inkovaara 1983	1	1	2	2	2	2	2	1	0
Ishida 2004	1	2	2	2	0	1	0	2	1
Komulainen 1998	2	2	0	1	0	0	0	1	1
Law 2006	1	2	1	1	0	0	0	1	2
Lips 1996	2	2	1	2	2	2	0	2	1
Lyons 2007	2	2	2	2	2	2	0	2	2

Table 4. Quality assessment scores (*Continued*)

Menczel 1994	1	1	0	1	0	0	0	1	0
Meyer 2002	0	2	2	2	2	2	0	1	2
Nuti 2006	1	2	1	2	2	2	0	2	2
Orimo 1994	2	1	2	2	2	2	0	2	2
Ott 1989	2	1	2	2	2	2	1	2	2
Peacock 2000	1	0	1	2	2	1	1	2	2
Pfeifer 2000	2	1	1	2	2	2	0	2	1
Porthouse 2005	2	2	0	2	0	0	0	2	2
Prince 2008	2	2	2	2	2	2	0	2	0
RECORD 2005	2	2	2	2	2	2	0	2	1
Sato 1997	1	1	2	2	2	2	0	2	1
Sato 1999a	1	1	2	1	2	2	0	2	1
Sato 1999b	1	2	0	2	0	0	0	2	1
Shiraki 1996	1	1	2	1	2	2	0	2	2
Smith 2007	1	2	1	0	2	2	0	2	0
Tilyard 1992	1	1	0	2	0	0	0	2	2
Trivedi 2003	2	2	2	2	2	2	2	2	0
Ushi-royama 2001	1	0	0	2	0	0	0	1	0

Table 4. Quality assessment scores (*Continued*)

WHI 2006	1	2	2	2	2	2	1	2	2

Effects of interventions

See Table 1 for a list of vitamin D synonyms and abbreviations. Duration of intervention and follow up are described in the 'Characteristics of included studies'. Due to the randomisation by cluster in Law 2006, the effective numbers of events and participants have been adjusted by the design effect for inclusion in the relevant meta-analyses (*see* Analysis 1.1; Analysis 1.4; Analysis 14.1; Analysis 14.4). Therefore the numbers used in these meta-analyses are lower than those reported in the trial. Throughout the text of the review, the number of participants analysed in each meta-analysis is reported.

Inkovaara 1983 compared vitamin D, calcium and vitamin D, calcium versus placebo. Data for fractures were reported, but it is unclear whether the data represent fractures or participants with fractures. Data have not been included in the appropriate meta-analyses. The authors commented that fractures were more common in the placebo group, but the difference was not statistically significant.

Results are presented for fractures for the different comparisons, followed by complications. Results are presented for hip fracture, non-vertebral fracture, vertebral fracture and any new fracture (where this is not covered by the previous three categories). Any new fracture includes all fractures.

Vitamin D alone versus placebo or no treatment

Ten trials (Avenell 2004; Harwood 2004; Law 2006; Lips 1996; Lyons 2007; Meyer 2002; Peacock 2000: RECORD 2005; Smith 2007; Trivedi 2003).

Pooled data comparing vitamin D alone with placebo or no treatment showed no statistically significant effect on hip fracture (nine trials, 24,749 participants, RR 1.15, 95% CI 0.99 to 1.33, Analysis 1.1), non-vertebral fracture (one trial, 3440 participants, RR 0.96, 95% CI 0.80 to 1.15, Analysis 1.2), vertebral fracture or deformity (five trials, 9138 participants, RR, random effects, 0.90, 95% CI 0.42 to 1.92, Analysis 1.3) or any new fracture (ten trials, 25,016 participants, RR 1.01, 95% CI 0.93 to 1.09, Analysis 1.4). There was evidence of very little heterogeneity (I^2 = 0%) in the trials reporting hip fracture. However there was some heterogeneity in the trials reporting new vertebral fracture or deformity (I^2 = 60%), which may have related to differences in fracture reporting, e.g. clinical event bringing participant to medical attention or routine x-ray follow up.

Vitamin D with calcium versus calcium alone

Eight trials (Avenell 2004; Bischoff 2003; Flicker 2005; Garay Lillo 1997; Komulainen 1998; Pfeifer 2000; Prince 2008; RECORD 2005).

In populations studied, vitamin D (including 25-hydroxy vitamin D) with calcium was no more effective than calcium alone on hip fracture (four trials, 6988 participants, RR 0.83, 95% CI 0.61 to 1.12, Analysis 2.1), any non-vertebral fracture (four trials, 3061 participants, RR 0.96, 95% CI 0.79 to 1.16, Analysis 2.2), vertebral fracture (two trials, 2681 participants, RR 0.14, 95% CI 0.01 to 2.77, Analysis 2.3), or any fracture (two trials, 927 participants, RR 0.76, 95% CI 0.48 to 1.21, Analysis 2.4).

Vitamin D versus calcium

Three trials (Avenell 2004; Peacock 2000; RECORD 2005).

There was no evidence of a statistically significant difference between vitamin D alone and calcium in the prevention of hip fracture (two trials, 2718 participants, RR 0.90, 95% CI 0.61 to 1.32, Analysis 3.1) or non-vertebral fractures (three trials, 2976 participants, RR 1.08, 95% CI 0.90 to 1.31, Analysis 3.2). There was evidence that vitamin D alone was less effective than calcium for the prevention of vertebral fracture or deformity (three trials, 2976 participants, RR 2.21, 95% CI 1.08 to 4.53, Analysis 3.3).

Vitamin D plus calcium versus placebo or no treatment

Hip fracture

Eight trials (Avenell 2004; Chapuy 1992; Chapuy 2002; Dawson-Hughes 1997; Harwood 2004; Porthouse 2005; RECORD 2005; WHI 2006).

Pooled data showed a statistically significant reduction in the incidence of hip fracture in the population receiving vitamin D and calcium (eight trials, 46,658 participants, RR 0.84, 95% CI 0.73 to 0.96, Analysis 4.1). Heterogeneity was not evident (I^2 = 0%). In the subgroup analyses by history of prior fracture, there was no evidence of a statistically significant reduction in effect of calcium and vitamin D (four trials, 6134 participants, RR 1.02, 95% CI 0.71 to 1.47), but the pooled data from studies where a previous

osteoporotic fracture was not a selection criterion did show a statistically significant reduction (four trials, 40,524 participants, RR 0.81, 95% CI 0.71 to 0.93). The difference between subgroups did not reach statistical significance (P = 0.24).
In the subgroup analysis by residential status (institution versus community: Analysis 4.2) there was a statistically significant reduction in hip fracture incidence in the institutional residents subgroup (two trials, 3853 participants, RR 0.75, 95% CI 0.62 to 0.92), but not in the community dwelling group (six trials, 42,805 participants, RR 0.91, 95% CI 0.76 to 1.08). However, there was no statistically significant difference between subgroups (P = 0.15).

Non-vertebral fracture

Nine trials (Avenell 2004; Bolton-Smith 2007; Chapuy 1992; Chapuy 2002; Dawson-Hughes 1997; Harwood 2004; Porthouse 2005; RECORD 2005; WHI 2006).
Overall, administration of vitamin D and calcium was not associated with a statistically significant reduction in incidence of new non-vertebral fracture (nine trials, 46,781 participants, RR 0.95, 95% CI 0.90 to 1.00, Analysis 4.3).
In the subgroup analyses by history of prior fracture there was no statistically significant reduction in non-vertebral fracture in participants selected on the basis of prior fracture (four trials 6134 participants, RR 0.93, 95% CI 0.79 to 1.10), or in participants not so selected (five trials, 40,647 participants, RR 0.95, 95% CI 0.90 to 1.01). There was no statistically significant difference between subgroups (P = 0.81).
In the subgroup analysis by residential status (institution versus community: Analysis 4.4) there was a statistically significant reduction in new non-vertebral fracture incidence in the institutional residents subgroup (two trials, 3853 participants, RR 0.85, 95% CI 0.74 to 0.98), but not in the community dwelling group (seven trials, 42,928 participants, RR 0.97 95% CI 0.91 to 1.02). There was no statistically significant difference between subgroups (P = 0.09).

Vertebral fracture

Three trials (Avenell 2004; RECORD 2005; WHI 2006).
There was no evidence of a statistically significant preventive effect on clinical vertebral fractures from the administration of vitamin D and calcium (three trials, 38,990 participants, RR 0.91, 95% CI 0.75 to 1.11, Analysis 4.5).

Alfacalcidol (1-alpha-hydroxy vitamin D3) versus placebo or no treatment

Hip fracture

Four trials (Ishida 2004; Sato 1997; Sato 1999a; Sato 1999b).
Alfacalcidol (1-alpha-hydroxy vitamin D3) was effective in reducing the incidence of hip fractures in older people with and without pre-existing osteoporotic fractures (four trials, 371 participants, RR 0.18, 95% CI 0.05 to 0.67, Analysis 5.1).

Non-vertebral fracture

Five trials (Dukas 2004; Gorai 1999; Ishida 2004; Sato 1999a; Ushiroyama 2001).
There was no statistically significant reduction in non-vertebral fractures in people with and without pre-existing osteoporotic fracture (five trials, 744 participants, RR 0.39, 95% CI 0.15 to 1.00, Analysis 5.2).

Vertebral fracture

One trial (Ishida 2004).
There was no statistically significant reduction in vertebral fractures (one trial, 132 participants, RR 0.65, 95% CI 0.33 to 1.27, Analysis 5.3).

Alfacalcidol (1-alpha-hydroxy vitamin D3) plus calcium versus calcium

Three trials (Menczel 1994; Orimo 1994; Shiraki 1996).
There was no statistically significant reduction in hip fractures (one trial, 113 participants, RR 0.20, 95% CI 0.01 to 4.00, Analysis 6.1) or on the development of new vertebral deformity (three trials, 259 participants, RR 0.50, 95% CI 0.20 to 1.23, Analysis 6.2).

Alfacalcidol (1-alpha-hydroxy vitamin D3) versus calcium

One trial (Geusens 1986) in participants with osteoporosis found no statistically significant effect of alfacalcidol (1-alpha-hydroxy vitamin D3) compared with calcium on people with new vertebral deformities (one trial, 23 participants, RR 0.95, 95% CI 0.52 to 1.74, Analysis 7.1).

Alfacalcidol (1-alpha-hydroxy vitamin D3) versus vitamin D and calcium

One trial (Nuti 2006) in participants with osteoporosis found no statistically significant effect of alfacalcidol (1-alpha-hydroxy vitamin D3) compared with vitamin D and calcium on people with new vertebral deformities (one trial, 148 participants, RR 0.81, 95% CI 0.29 to 2.30, Analysis 8.1).

Calcitriol (1,25 dihydroxy vitamin D3) versus placebo or no treatment

Three trials (Caniggia 1984; Gallagher 1989; Gallagher 2001). Calcitriol had no statistically significant effect on hip fracture (one trial, 246 participants RR 0.33, 95% CI 0.01 to 8.10, Analysis 9.1), non-vertebral fracture (one trial, 246 participants, RR 0.46, 95% CI 0.18 to 1.18, Analysis 9.2), or new vertebral deformity (three trials, 327 participants RR 0.75, 95% CI 0.40 to 1.41, Analysis 9.3).

Calcitriol (1,25 dihydroxy vitamin D3) plus calcium versus calcium

Additional supplementation with calcitriol in people with osteoporosis already taking calcium (Ott 1989) showed no statistically significant effect on the incidence of new vertebral deformity (86 participants, RR 1.50, 95% CI 0.58 to 3.85, Analysis 10.1).

Calcitriol (1,25 dihydroxy vitamin D3) plus vitamin D and calcium versus vitamin D and calcium

Two studies (Aloia 1988; Gallagher 1990), found no statistically significant effect on the number of people developing new vertebral deformities (two trials, 84 participants RR 0.79, 95% CI 0.41 to 1.52, Analysis 11.1).

Calcitriol (1,25 dihydroxy vitamin D3) versus calcium

Two trials (Ebeling 2001; Tilyard 1992).
Overall, there was no statistically significant effect on the incidence of non-vertebral fractures (two trials, 663 participants, random-effects RR 1.19, 95% CI 0.09 to 15.77, Analysis 12.1) or vertebral deformities (two trials, 556 participants, random-effects RR 1.69, 95% CI 0.25 to 11.28, Analysis 12.2).
In Tilyard 1992 the duration of treatment was critical (*see* Analysis 12.3). At the end of one year, no effect could be shown. Fewer vertebral deformities occurred in the calcitriol group during the second year (RR 0.47, 95% CI 0.26 to 0.87), and during the third year (RR 0.28, 95% CI 0.15 to 0.52).

Calcitriol (1,25 dihydroxy vitamin D3) versus vitamin D

Two trials (Arthur 1990; Falch 1987).
When calcitriol was compared with vitamin D in people with pre-existing osteoporosis no statistically significant effect was seen for non-vertebral fractures (one trial, 86 participants, RR 1.16, 95% CI 0.40 to 3.37, Analysis 13.1) or vertebral deformities (two trials, 96 participants RR 1.38, 95% CI, 0.55 to 3.47, Analysis 13.2).

Reported adverse effects: vitamin D [D2, D3 or 25(OH)D] or any analogue with/without calcium

Hypercalcaemia

Eighteen trials (Aloia 1988; Avenell 2004; Bischoff 2003; Chapuy 2002; Dukas 2004; Gallagher 2001; Gorai 1999; Harwood 2004; Law 2006; Menczel 1994; Orimo 1994; Ott 1989; Peacock 2000; Prince 2008; RECORD 2005; Sato 1999b; Tilyard 1992; Ushiroyama 2001).
Hypercalcaemia was reported more commonly when vitamin D or its analogues were given compared with placebo or calcium (18 trials, 11,346 participants, RR 2.35, 95% CI 1.59 to 3.47, Analysis 14.1). The risk of hypercalcaemia was particularly high for the use of calcitriol (four trials, 988 participants, RR 4.41, 95% CI 2.14 to 9.09, Analysis 14.1.4).

Gastrointestinal symptoms

Eleven trials (Avenell 2004; Bischoff 2003; Chapuy 1992; Chapuy 2002; Ebeling 2001; Gallagher 2001; Nuti 2006; Prince 2008; RECORD 2005; Tilyard 1992, WHI 2006).
There was evidence of a small increase in gastrointestinal symptoms (11 trials, 47,042 participants, RR 1.04, 95% CI 1.00 to 1.08, P = 0.04, Analysis 14.2).

Occurrence of renal calculi or renal insufficiency

Eleven trials (Aloia 1988; Avenell 2004; Chapuy 2002; Gallagher 1990; Gallagher 2001; Menczel 1994; Nuti 2006; Peacock 2000; RECORD 2005; Tilyard 1992; WHI 2006).
There was evidence of a statistically significant increase in the incidence of renal calculi or renal insufficiency (11 trials, 46,537 participants, RR 1.16, 95% CI 1.02 to 1.33, Analysis 14.3).

Deaths

The risk of death during the studies appeared marginally lower in participants given vitamin D or its analogues with or without calcium than in those given placebo or calcium, but the difference was not statistically significant (23 trials, 64,423 participants, RR 0.97, 95% CI 0.93 to 1.01, Analysis 14.4).
Subgroup analysis by residential status (institution versus community) of the studies in which participants had received calcium and vitamin D showed no difference between subgroups (Analysis 15.1, P = 0.86).
Table 3 lists adverse effects reported in trials of interventions meeting the inclusion criteria that were excluded because they did not report fracture data.

DISCUSSION

This update includes data from eight new trials, with 44,827 participants, including a number of large community-based studies.

Summary of main results

Vitamin D alone versus placebo or no treatment

The following discussion presumes that intermittent dosing can be approximately equated to daily dosing, although it is not clear if this is the case. There was no protective effect against fractures from an annual injection of vitamin D2 alone (equivalent to approximately 830 IU daily) in the prevention of hip or other osteoporotic fractures in older people (Harwood 2004; Smith 2007). Oral intermittent bolus administration of vitamin D alone, either as vitamin D2 (approximately 830 to 1100 IU daily) or vitamin D3 (approximately 830 IU daily) (Law 2006; Lyons 2007; Trivedi 2003), does not appear to protect against osteoporotic fractures, in people with or without a previous osteoporotic fracture. Nor does a daily dose of up to 830 IU of vitamin D3 (Avenell 2004; Harwood 2004; Lips 1996; Meyer 2002; RECORD 2005). However, further studies may be indicated with doses of at least 1100 IU daily as vitamin D3 in very high risk populations with low sunlight exposure, such as people in nursing homes.

Vitamin D plus calcium versus placebo or no treatment

Overall, the pooled data continue to indicate that the administration of 400 to 800 IU vitamin D3 with co-administration of 1000 mg calcium reduces the incidence of hip fractures but not of all non-vertebral fractures in the populations studied. The very large WHI 2006 used a lower dose of 400 IU vitamin D and 1000 mg calcium and showed a trend only for hip fracture reduction. Higher doses of vitamin D3 than 400 IU would appear more effective.

We conducted two subgroup analyses. The first separated the data by the residential status of the participants at recruitment. We defined institutional as residence in a nursing home or residential care home. We recognise that differences exist in nomenclature between different countries, but found the descriptions provided by trialists sufficient to make a judgement in most cases. Studies with a mixed population were categorised as institutional or community based on the dominant place of residence of participants. For example, we classified RECORD 2005 as a community study as 94% of participants were resident in their own homes and only 6% were resident in institutions. This subgroup analysis was not pre-defined in the original review in 1995, but emerged for an earlier update from the accumulation of evidence, from clinical biochemistry and epidemiology, that many frail institutionalised older people are vitamin D deficient, particularly in the winter months, when the incidence of hip fracture is highest (Boonen 1996; LeBoff 1999). We hypothesised that they, in particular, may benefit from the administration of vitamin D and calcium. The results of the subgroup analysis (and indeed of the overall analysis) offer limited support to that hypothesis; although the difference between the subgroups is not significant, a statistically significant effect is seen in the pooled data from the institutionalised participants, but not in those living in the community. This analysis is particularly influenced by the two trials (Chapuy 1992; Chapuy 2002) conducted amongst frail people living in nursing homes or apartments for older people in France.

Considerable epidemiologic evidence supports the association between prior osteoporotic fracture and subsequent hip fracture; RECORD 2005 therefore recruited participants with a prior fracture history. We found no evidence from our subgroup analysis (which is heavily dominated by RECORD 2005), that a population with such a history, irrespective of age, benefits in respect of hip fracture incidence from vitamin D and calcium. Although the dose of vitamin D3 used in RECORD 2005 was the same as Chapuy 1992 and Chapuy 2002, poorer compliance may have reduced the effect. Ways to improve compliance with bone active medication of all forms in this population need researching (Seeman 2007).

Alfacalcidol

Four small trials of alfacalcidol, of which three were in Japan by the same author (Sato 1997; Sato 1999a; Sato 1999b) suggest that hip fractures may be prevented. Positive results from these small studies need to be confirmed by other investigators. Other small studies, which compared alfacalcidol with calcium (with or without vitamin D), or alfacalcidol and calcium with calcium, were inconclusive.

Calcitriol

The effect of calcitriol in fracture prevention is unclear, with the best evidence for effectiveness coming from the trial of Tilyard 1992 comparing calcitriol with calcium where vertebral deformities were significantly reduced only in the second and third years. However, the use of calcitriol is associated with a statistically significantly increase in risk of hypercalcaemia.

Adverse effects

In the past there has been serious concern that cholecalciferol or ergocalciferol may be associated with hypercalcaemia when given in only moderate doses, which may have led to cautious use of low doses in the trials of vitamin D. There is increasing evidence that potential toxicity in this respect has been seriously overestimated, and that requirements for vitamin D3 may be more than

previously recognised (Vieth 2001). Gastrointestinal effects and renal disease (especially calculi) were more common amongst participants receiving vitamin D. This analysis is dominated by WHI 2006, in which calcium supplements were also given, but there is no significant difference between the subgroups with and without calcium supplementation.

Overall completeness and applicability of evidence

Despite the ability of injection of vitamin D to reduce the winter decline in serum vitamin D concentrations (Khaw 1994) and the apparently positive findings of Heikinheimo 1992, there is robust evidence that the administration of Vitamin D alone, whether by annual injection, periodic bolus oral dosage, or daily oral dosage, is unlikely to be effective in fracture prevention in doses below 1100 IU daily (ten trials, 25,016 participants, RR 1.01, 95% CI 0.93 to 1.09). The results of the ongoing Vital D study, which is examining the use of 500,000 IU vitamin D3 annually as an oral dose in a high risk population (which could equate to approximately 1400 IU daily), should help in this regard.

However, there is evidence supporting the hypothesis, examined in a pre-planned subgroup analysis, that Vitamin D in doses of 700-800 IU daily, with co-administration of 1000 mg calcium, is effective in reducing the rate of hip fractures in frail older people in institutional care (two trials, 3853 participants, RR 0.75, 95%CI 0.62 to 0.92). Both these studies, reported 10 years apart, were from the same research group in France. It remains unclear whether the results are generalisable to other health and social care systems. Further trials in similar settings in other countries would be valuable, although the widespread adoption of use of vitamin D and calcium in these settings, based on these two studies, might raise ethical issues, making further placebo-controlled trials difficult to carry out.

A larger body of evidence from the UK and USA, again synthesised in a pre-planned subgroup analysis, suggests that administration of Vitamin D with co-administration of calcium may not be effective when offered to older people living in the community (six trials, 42,805 participants, RR 0.91, 95% CI 0.76 to 1.08). This is a reasonably robust finding. Given the greater costs per person of this combined regimen, and the continuing doubt about its effectiveness in this setting, its implications require thoughtful consideration. Some caution is required in the interpretation of these results as the risk ratios for the two subgroups were not statistically significantly different.

The marginal reduction in risk of death in people receiving vitamin D with calcium is consistent with the reduction in hip fracture risk, since hip fracture in frail older people is associated with increased mortality in the first three months after fracture (Rapp 2008). However, we have not demonstrated a significant reduction in mortality in the overall analysis (Analysis 14.4), or a significant difference between the subgroups within that analysis.

We note the effectiveness of alfacalcidol in fracture prevention in older people with neurologic disorders in the three studies from Japan (Sato 1997; Sato 1999a; Sato 1999b). It remains unclear whether the results are generalisable to other health and social care systems. Further trials in similar settings in other countries would be valuable.

Potential biases in the review process

We believe that selection bias is unlikely in this review. We have searched a wide range of databases and handsearched numerous relevant journals. We note, though, that we have identified 14 reports of studies which may if further information becomes available, be eligible for inclusion. The contact author is in touch with major research groups in this field. Action was taken to minimise bias in the selection of studies for inclusion, and during the process of quality assessment and data extraction, as recommended in the Cochrane Handbook. Authors who had participated in included trials (AA and WJG) were not involved in the quality assessment or data extraction relating to those studies.

However the reporting of adverse effects (Analyses 14.1 to 14.4) includes only RCTs in which vitamin D or vitamin D analogues have been administered to evaluate their effect on fractures or surrogate outcomes such as bone mineral density (BMD). Our search strategy was not designed to identify studies in which vitamin D was administered for other reasons. Nor would it have identified other study types which might have provided useful data on adverse effects. So, the data used in these analyses is incomplete, although there is no reason to suspect that it is not representative.

Ascertainment bias cannot be completely ruled out. Incomplete information was available to us on the number of drop outs from intervention and control groups in a number of trials. Thus, it is possible that our analyses, based on the principles of intention-to-treat, might have under estimated the number of outcome events in the intervention or control groups, or both. But on balance, this may not be a critical matter.

What is the correct dose of vitamin D3 to use?

There is growing discussion that a serum 25(OH) vitamin D3 level in the range of 50-80 nmol/L may be optimal for fracture prevention (Bischoff-F 2006; Dawson-Hughes 2005; Vieth 2007), although there is no universal consensus (Francis 2008). There is a need to establish what the optimal serum 25(OH) vitamin D3 level should be, as well as the dose of vitamin D3 supplementation required to achieve this. The doses provided in the trials in this review might not have been adequate. Insufficient vitamin D, vitamin D2 rather than vitamin D3, and/or poor compliance might have affected the results of some of the trials included in this review. A higher annual dose of 500,000 IU is being tested in

the Vital D study, which is higher than any of the doses used in the trials included in this review (average 1400 IU vitamin D3/day).

Baseline vitamin D levels

Table 5 gives the baseline 25(OH) vitamin D levels in the intervention and control groups of the included studies. The values have to be interpreted with caution, since they depend on the laboratory and method used (Lips 1999). It might be expected that those people with the lowest 25(OH) vitamin D levels would benefit most from supplementation, and there is some suggestion of this in Chapuy 1992 (25(OH)D of 40 nmol/L) and Chapuy 2002 (22 nmol/L). Lips 1996 (27 nmol/L) also had low values but had a lower dose of supplementation of 400 IU vitamin D3 daily. The results of the RECORD 2005 trial are somewhat contradictory, given the 25(OH) vitamin D3 level of 38 nmol/L. The statistically significant result for all fractures from the trial of Dawson-Hughes 1997 is also unusual given the high average baseline value of 77 nmol/L. However, it has been argued that adequate 25(OH) vitamin D levels of at least 75 nmol/L are required to suppress parathyroid hormone and bone turnover (Dawson-Hughes 2005).

Table 5. Baseline 25(OH)D in intervention and control groups

Study ID	25(OH)D nmol/L
Aloia 1988	Intervention 54.8 (SD 17.8); Control 66.5 (SD 29.3)
Arthur 1990	Intervention 30 (SD 7.5); Control 52.5 (SD 22.5)*
Avenell 2004	N/A
Bischoff 2003	Intervention 30.8 (interquartile range 23-55); Control 29 (interquartile range 23-55)
Bolton-Smith 2007	Intervention 62.5 (SD 15.5); Control 57 (15.3)
Caniggia 1984	N/A
Chapuy 1992	Intervention 40.0 (SD 27.5); Control 32.5 (SD 22.5) subgroups
Chapuy 2002	Intervention 21.3 (SD 13.3), 22.5 (SD 16.5); Control 22.8 (SD 17.3)
Dawson-Hughes 1997	Intervention 82.5 (SD 40.8) men, 71.8 (SD 33.3) women; Control 84.0 (SD 31.8) men, 61.3 (SD 25.8) women
Dukas 2004	Intervention 98.8 (SD 30.0); Control 97.8 (SD 27.3)*
Ebeling 2001	Intervention 91 (SD 42); Control 86 (27)
Falch 1987	N/A

Table 5. Baseline 25(OH)D in intervention and control groups (*Continued*)

Flicker 2005	Intervention 61% in 25-40 range; Control 54% in 25-40 range
Gallagher 1989	N/A
Gallagher 1990	N/A
Gallagher 2001	Intervention 78.0 (SD 21.6); Control 80.5 (SD 27.4)
Garay Lillo 1997	Intervention 58.3 (SD 46.3); Control 64.8 (SD 51.3) subgroups
Geusens 1986	N/A
Gorai 1999	N/A
Harwood 2004	Intervention 28 (range 10-67), 30 (range 12-85), 29 (range 6-75); Control 30 (range 12-64)
Inkovaara 1983	N/A
Ishida 2004	N/A
Komulainen 1998	N/A
Law 2006	Intervention 47 median (35-102, 90th centile range) subgroup; no data for control group
Lips 1996	Intervention 27 (25th-75th centile 19-36); Control 26 (25th-75th centile 19-37) subgroups
Lyons 2007	N/A
Menczel 1994	N/A
Meyer 2002	Intervention 47 (SD 26); Control 51 (SD 33) subgroups
Nuti 2006	Intervention 60.14 (SD 23.07); Control 57.80 (SD 17.32)*
Orimo 1994	Intervention 58.0 (SD 22.5); Control 50.3 (SD 16.3)
Ott 1989	Intervention 66.8 (SD 31.5); Control 65.8 (SD 39.3)
Peacock 2000	Intervention 65.0 (SD 25) men, 57.5 (SD 33) women; Control 65.0 (SD 30) men, 60.0 (SD 30) women
Pfeifer 2000	Interventiion 25.7 (SD 13.6); Control 24.6 (SD 12.1)
Porthouse 2005	N/A
Prince 2008	Intervention 45.2 (SD 12.5); Control 44.3 (SD 12.7)
RECORD 2005	Intervention 38.0 (SD 16.3); Control 39.5 (SD 14.8) subgroups*

Table 5. Baseline 25(OH)D in intervention and control groups (*Continued*)

Sato 1997	N/A
Sato 1999a	Intervention 27.5 (SD 14.8); Control 29.5 (SD 17.3)
Sato 1999b	Intervention 28.5 (SD 11.7); Control 30.2 (SD 13.7)
Shiraki 1996	N/A
Smith 2007	Intervention 56.5; Control 62.2 subgroups
Tilyard 1992	N/A
Trivedi 2003	N/A
Ushiroyama 2001	N/A
WHI 2006	46.0 (SD 22.6) subsequent hip fracture, 48.4 (SD 23.5) controls, subgroups

* reported as D3

Agreements and disagreements with other studies or reviews

Since the last version of this review several other systematic reviews have been published on related topics. Richy 2005 indirectly compared (using different criteria for study inclusion) vitamin D analogues with vitamin D for prevention of bone loss and fractures in people with primary osteoporosis and osteoporosis secondary to glucocorticoids. The influence of calcium was not examined, and no direct comparisons were provided for involutional and post-menopausal osteoporosis. Richy 2005 reported that alfacalcidol and calcitriol were more effective at preventing fractures than vitamin D. In our review Arthur 1990 and Falch 1987 compared calcitriol with vitamin D (calcium was given to both groups in Arthur 1990). We found no significant difference between the two forms of vitamin D.

A systematic review by Bischoff-Ferrari et al (Bischoff-F 2005) concluded that oral vitamin D supplementation between 700 to 800 IU daily appeared to reduce the risk of hip and any non-vertebral fractures in ambulatory or institutionalised older people. Trials of vitamin D both with and without calcium supplementation were included in a single analysis, and Porthouse 2005, RECORD 2005 and Smith 2007 were not included in the analyses. A more recent meta-analysis by Boonen 2007, which included the WHI 2006 study, examined calcium and vitamin D separately from vitamin D alone and concluded that calcium was needed in addition to vitamin D, as we have found.

Autier 2007 recently undertook a meta-analysis of randomised controlled trials of vitamin D supplementation for any indication and the effect on mortality. They found that vitamin D reduced all cause mortality (RR 0.93, 95% CI 0.87 to 0.99). In our review we found an overall risk ratio of 0.97 (95% CI 0.93 to 1.01). The inclusion criteria for the two reviews were different, and our literature search update was more recent. Autier 2007 included data from fewer participants, and excluded studies examining either alfacalcidol or calcitriol. In our review, removal of trials using alfacalcidol or calcitriol from Analysis 14.4 did not change the overall result (RR 0.97, 95% CI 0.93 to 1.01: analysis not shown).

AUTHORS' CONCLUSIONS

Implications for practice

Frail older people confined to institutions appear to experience a

reduction in hip and other non-vertebral fractures if given vitamin D with calcium supplements.

The effectiveness in fracture prevention of administration of vitamin D with calcium supplements to community-dwelling older people is unclear.

Supplementation with vitamin D and calcium, for fracture prevention, may be associated with a marginal reduction in mortality compatible with the reduction in hip fracture risk.

Vitamin D alone, in the doses which have been used, appears unlikely to be effective in fracture prevention in older people.

There is no evidence that related vitamin D compounds (analogues) have advantages in terms of effectiveness or reduced incidence of adverse effects compared with vitamin D.

Calcitriol appears to be associated with an increased incidence of adverse effects such as hypercalcaemia.

Implications for research

Although there could be important ethical considerations, the case might be made for large multi-centre placebo-controlled trials of vitamin D3 and calcium in institutional settings, informed by dose-finding studies.

Dose-finding studies are needed in different populations for vitamin D3, using preparations that are most likely to enhance compliance.

An individual patient data synthesis from the published studies of effectiveness of vitamin D with calcium could add some precision to the data available by identifying the institutional dwelling participants from studies with mixed populations. Two such syntheses are underway, being led by groups from Europe and the USA (Abrahamsen 2007; Dawson-Hughes 2008).

The design and reporting of any future trials should conform to the CONSORT statement (Moher 2001) or any future development of it. Trials using cluster randomisation should perform appropriate analyses and include sufficient information in trial reports to aid interpretation by readers and users of such trials (Campbell 2004).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aloia 1988

Methods	Randomisation schedule held off campus by the sponsoring manufacturer. Appears adequately blinded. 27 of 34 completed.
Participants	Tertiary hospital. USA. 34 women with post menopausal osteoporosis aged 50-80 yr. (Mean age 64.5 yr). Sample drawn from media release publicity. Inclusion criterion: at least one non-traumatic vertebral compression fracture. Disease exclusions: hepatic or renal disease, malignancy, malabsorption, parathyroid or thyroid disorder, inflammatory arthritis, alcoholism, overt vitamin D deficiency, history of renal stones, insulin dependent diabetes, previous long term hospitalisation, any other disorder known to affect bone metabolism. Drug exclusions: glucocorticoids, anticonvulsants, oestrogens, sodium fluoride, calcium supplements, pharmacologic doses of vitamin D.
Interventions	1. Calcitriol 0.25 mcg, dose titrated, plus vitamin D 400 IU daily. Randomised 17, completed 12. 2. Placebo plus vitamin D 400 IU daily. Randomised 17, completed 15. Calcium intake adjusted to 1 g per day in each group (diet adjustment). Stepwise increase at two weekly intervals ending at double the initial dose permitted at investigators control. Duration of treatment 24 months.
Outcomes	Measured at 2 years. 1. Number of women with new vertebral fractures, measured radiologically. 2. Number of new vertebral fractures in each group. 3. BMC radius. 4. BMD lumbar spine. 5. Total body calcium (neutron activation). 6. Radiographic absorptiometry of phalanges. 7. Urinary hydroxyproline. 8. Vitamin D metabolites. 9. PTH radioimmunoassay. 10. Serum alkaline phosphatase. 11. Serum osteocalcin. 12. Bone biopsy. 13. Renal dysfunction.
Notes	Although authors published separately, trial protocol was identical with Gallagher 1990 and Ott 1989 (*see* personal communication from Gallagher under Aloia 1988)

Risk of bias

Item	Authors' judgement	Description

Aloia 1988 (*Continued*)

Allocation concealment?	Yes	A - Adequate

Arthur 1990

Methods	Randomised trial of two treatments. Normal "controls" described but not randomised. Radiologic assessors blinded. 10 of 14 completed.
Participants	Community hospital, USA. 10 women over 60 yr (mean age 66.5 yr) with radiographic and bone biopsy evidence of osteoporosis. Disease exclusions: renal or liver disease, malabsorption or surgery that might predispose to malabsorption, hypercalcaemia, malignancy, hyperthyroidism, alcoholism, significant immobilisation. Drug exclusions: use of steroids (including oestrogen), heparin or anticonvulsants.
Interventions	1. Calcitriol 0.25 mcg plus 1 g elemental calcium per day orally. Calcitriol dose doubled in all patients by end of study (monitored by serum calcium at 10 mg/dl or less). Randomised 7, completed 4. 2. Ergocalciferol 50,000 units orally twice weekly, plus 1 g elemental calcium daily. Randomised 7, completed 6. All in Group 1 and two thirds in Group 2 were taking calcium supplements at entry. Duration of treatment 12 months.
Outcomes	Measured at 1 year. 1. Women sustaining new vertebral fractures during study. 2. BMD lumbar spine (CT). 3. Bone biopsy. 4. Serum vitamin D. 5. Serum Ca, PO4, creatinine. 6. Creatinine clearance. 7. Daily calcium excretion.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Avenell 2004

Methods	Random allocation. Remote site computer randomisation. Blinding of outcome assessors stated. 106 of 134 completed.
Participants	Community-based study, United Kingdom. 134 patients (111 women, 23 men). Inclusion criteria: osteoporotic fracture within the last ten years, aged 70 years or over. Disease exclusion: bed or chair bound prior to fracture, cognitive impairment indicated by an abbreviated mental test score of under seven, suffered from cancer likely to metastasise to bone within the previous ten years, fracture associated with pre-existing local bone abnormality, known hypercalcaemia, renal stone in the last 10 years, life expectancy less than six months, known to be leaving the UK. Drug exclusions: taking more than 200 IU (5 mcg) vitamin D or more than 500 mg calcium supplements daily; had fluoride, bisphosphonates, calcitonin, tibolone, hormone replacement therapy, selective estrogen receptor modulators, or any vitamin D metabolite (such as calcitriol)in the last 5 years; vitamin D by injection in the last year.
Interventions	1. Calcium 1000 mg and vitamin D3 800 IU given as two tablets daily. Randomised 35, completed 32. 2. Calcium 1000 mg given as two tablets daily. Randomised 29, completed 25. 3. Vitamin D3 800 IU given as two tablets daily. Randomised 35, completed 20. 4. No tablets. Randomised 35, completed 29. Duration of treatment up to 46 months.
Outcomes	Measured over 46 months. 1. Number of persons sustaining new hip fracture. 2. Number of persons sustaining new non-vertebral fracture. 3. Number of persons with new clinical vertebral fracture. 4. Number of persons with hypercalcaemia, renal stone or failure, gastrointestinal adverse events. 5. Numbers of persons dying.
Notes	Dr Avenell provided longer-term follow-up data (one year data in published trial). Trial is parallel study to RECORD trial.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Bischoff 2003

Methods	Statistician generated block randomisation, no further details. Double-blind trial. Losses to follow up at 12 weeks for fracture data of 33 of 122 (27%).
Participants	Two long-stay geriatric care units, Switzerland. 122 patients (all women), mean age 85.3 yr (SD 6.6). Inclusion criteria: 60 years or over, ability to walk 3 meters with or without walking aid.

Bischoff 2003 (*Continued*)

	Disease exclusions: primary hyperparathyroidism, hypocalcaemia, hypercalciuria, creatinine > 117 mcmol/L, fracture or stroke in last 3 months. Drug exclusions: hormone replacement therapy, calcitonin, fluoride, bisphosphonates in last 24 months.
Interventions	1. 1200 mg calcium carbonate and 800 IU vitamin D3 as two tablets daily. Randomised 62, 43 completed 12 weeks. 2. 1200 mg calcium carbonate as two tablets daily. Randomised 60, 45 completed 12 weeks. Duration of treatment 12 weeks.
Outcomes	Measured over a follow up of 12 weeks. 1. Number of persons with new hip fracture. 2. Number of persons with gastrointestinal adverse events, hypercalcaemia. 3. Numbers of persons dying.
Notes	Dr Bischoff supplied hip fracture and mortality data according to allocation by e-mail on 13.07.2003.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Bolton-Smith 2007

Methods	Double-blind trial. Independent statistician at remote site provided randomisation. Losses to follow up at 2 years for fracture data of 17 of 123 (14%) for vitamin D/calcium group and placebo group only.
Participants	123 patients (all women), mean age 68.6 yr, for vitamin D/calcium group and placebo group only. Inclusion criterion: 60 years or over, healthy. Disease exclusions: clinical osteoporosis; chronic disease (e.g. diabetes mellitus, cardiovascular disease, cancer, fat malabsorption); Drug exclusions: routine medication interfering with vitamin K, vitamin D or bone metabolism (e.g. warfarin, steroids); supplements over 30 mcg/d vitamin K, 10 mcg (400 IU)/d vitamin D or 500 mg calcium/d.
Interventions	1. 1000 mg calcium carbonate and 400 IU vitamin D3 daily and placebo daily. Randomised 62, 50 completed 2 years. 2. 1000 mg calcium carbonate and 400 IU vitamin D3 and 200 mcg vitamin K1 daily. 3. 200 mcg vitamin K1 daily and placebo daily. 4. Double placebo. Randomised 61, 56 completed 2 years. Duration of treatment 2 years.
Outcomes	Measured over a follow up of 2 years. 1. Number of persons with new non-vertebral fracture

Bolton-Smith 2007 (*Continued*)

Notes	Prof McMurdo supplied fracture data, collected by self-report, on 1.10.2007. Groups 2 and 3 not used in this review.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Caniggia 1984

Methods	Allocation concealment technique not clearly described, nor clarified as result of correspondence. Blinding appears adequate. 22 of 28 completed.
Participants	Tertiary hospital. Italy. 28 women aged 54 to 74 yr (mean age not given) with symptomatic post-menopausal osteoporosis. Inclusion criterion: radiolucency of spine with at least one crush fracture. Disease exclusions: osteomalacia on iliac crest bone biopsy, malabsorption. Drug exclusions: adrenocorticosteroids from 3 months or more in last 5 years, anticonvulsants, oestrogens, progestagens, androgens, anabolic drugs (in last 6 months), chlorothiazide and allied diuretics, sodium fluoride, calcium and vitamin D within the last 6 months.
Interventions	1. 1,25(OH)2 vitamin D3 0.5 mcg /day with estrogen placebo. Randomised 7, completed 5. 2. Estradiol valerate 2 mg per day on 21 on and 7 off cycle, with Vitamin D3 placebo. Randomised 7, completed 5. 3. Both interventions as in 1 and 2. Randomised 7, completed 7. 4. Double placebo. Randomised 7, completed 5. Duration of treatment 1 year.
Outcomes	Measured at 1 year. 1. Number of new vertebral fractures. 2. Variation in standing height. 3. BMC of the ulna at two measuring points. 4. Iliac crest bone histomorphometry. 5. Pain relief and improvement of mobility. 6. Biochemical parameters: plasma and urinary calcium, phosphate, and creatinine, serum alkaline phosphatase, urinary hydroxyproline, liver enzymes, ESR. 7. Blood pressure, vaginal bleeding.
Notes	Clarification sought. Reply received.

Risk of bias

Caniggia 1984 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Chapuy 1992

Methods	Random allocation. Allocation concealment details following clarification from author. Blinding of assessors unclear. 2790 of 3270 available for intention to treat at 18 months. 2303 followed to three years.
Participants	France. 3270 women aged 69 to 106 yr (mean 84 SD 6) living in nursing homes or apartment houses for the elderly. Inclusion criteria: ambulant, life expectancy of at least 18 months. Previous fracture and thiazide usage not excluded. Disease exclusions: "serious medical conditions". Drug exclusions: corticosteroids, anticonvulsants, thyroxine, fluoride, calcium supplementation.
Interventions	1. Calcium 1.2 g plus vitamin D3 800 IU orally daily. Randomised 1634, 877 completed 18 months. 2. Double placebo. Randomised 1636, 888 completed 18 months. Treatment period 18 months for initial report, continued to complete three years.
Outcomes	1. Hip fractures at 18 months and 3 years. 2. Non-vertebral fractures at 18 months and 3 years. 3. In a subgroup, serum calcium,phosphate, creatinine, total protein, alkaline phosphatase, PTH,25-OHD3.(73 treatment, 69 placebo) at base line and six monthly to 18 months. 4. Femoral BMD at base line and after 18 months in 27 treatment and 29 placebo. 5. Adverse effects: gastro intestinal symptoms, renal disease, death.
Notes	Falling status recorded at base line but no falling data presented in the relevant papers thus far. Allocation concealment details provided following clarification from author. 18 month follow up reported in 1992, and three year follow up in 1994. There appears to be a discrepancy between the 18 month and three year report compatible with misclassification of five subjects at some point.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Chapuy 2002

Methods	Random allocation. No further details. Double-masked, placebo-controlled study, blinding of outcome assessors not confirmed. Losses to follow up at 24 months 188 of 610.
Participants	Residents of 55 apartment houses for elderly people, France. 610 women, mean age 85 years. Inclusion criteria: ambulatory (able to walk indoors with cane or walker), life expectancy of at least 24 months. Disease exclusions: intestinal malabsorption, hypercalcaemia (serum calcium > 2.63 mmol/L), chronic renal failure (serum creatinine > 150 mcmol/L). Drug exclusions: received drugs known to alter bone metabolism, such as corticosteroids, anticonvulsants or a high dose of thyroxine, in the past year. Fluoride salts (> 3 months), bisphosphonates, calcitonin (> 1 month), calcium (> 500 mg daily), vitamin D (> 100 IU daily) in last 12 months.
Interventions	1. Calcium 1200 mg as tricalcium phosphate and vitamin D3 800 IU daily as one sachet. 2. Calcium 1200 mg as tricalcium phosphate sachet and two pills of vitamin D3 400 IU daily. Groups 1 and 2: randomised 389, completed unclear. 3. One placebo sachet and two placebo tablets daily. Randomised 194, completed unclear. Duration of treatment 2 years.
Outcomes	Measured over a follow up of two years. 1. Number of persons sustaining new hip fracture. 2. Number of persons sustaining new non-vertebral fracture. 3. Numbers of persons developing hypercalcaemia. 4. Number of persons dying. 5. Number of persons reporting gastrointestinal disorders. 6. PTH, 25(OH) vitamin D. 7. Bone mineral density of distal radius, femoral neck bone mineral density, ultrasound of os calcis.
Notes	Prof Meunier provided further details on outcomes 28/02/2005

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Dawson-Hughes 1997

Methods	Random allocation. Stratified by gender, race, and decade of age. 389 of 445 completed.
Participants	Community-based study, USA. 445 enrolled participants (199 men, 246 women, aged 65 years and older (mean age 71 years). Recruitment was from a mix of volunteers answering advertisement, and presentations on medical care. Exclusion criteria: current cancer or hyperparathyroidism, renal stone history within five years, bilateral hip surgery, femoral neck BMD more than 2 SD below the mean for age and gender, dietary calcium intake exceeding 1500 mg per day, laboratory evidence of renal or liver disease.

Dawson-Hughes 1997 (*Continued*)

	Drug exclusions: therapy with a bisphosphonate, calcitonin, estrogen, tamoxifen, or testosterone in the past six months, or fluoride within the past two years.
Interventions	1. Calcium 500 mg plus vitamin D3 700 IU orally daily. 2. Double placebo. Total randomised 445, 389 completed. Duration of treatment 3 years.
Outcomes	Final assessment at three years. 1. Non-vertebral fractures identified by self report, interview, and validation from case records. Also measured at 6 month intervals, but not considered in this review, were bone mineral density, biochemical assays, and other measures.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Dukas 2004

Methods	Random allocation. Randomisation independent of trial. Blinding of outcome assessors stated. 323 of 380 completed.
Participants	Community study, Switzerland. 380 (192 women, 188 men), mean age 75 years. Inclusion criteria: age 70 years or over, mobile, independent lifestyle. Disease exclusions: primary hyperparathyroidism, polyarthritis, inability to walk, active kidney stone disease, history of hypercalciuria, cancer or other incurable disease, dementia, elective surgery within next 3 months, creatinine clearance < 20 ml/min, fracture or stroke in last 3 months. Drug exclusions: current calcium supplementation of > 500 mg/day or vitamin D > 200 IU/day.
Interventions	1. Alfacalcidol D3 one mcg tablet/day. Randomised 193, completed unclear. 2. Placebo tablet once daily. Randomised 187, completed unclear. Duration of treatment 36 weeks.
Outcomes	Measured over follow up of 36 weeks. 1. Number of persons sustaining new non-vertebral fracture. 2. Numbers of persons dying. 3. Numbers of persons developing hypercalcaemia. 4. PTH, 1,25(OH)2 and 25(OH)vitamin D3.
Notes	Dr LC Dukas provided fracture data 19/07/2004.

Dukas 2004 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Ebeling 2001

Methods	Random allocation. Outcome assessors blinded for assessment of vertebral fractures. 33 of 41 completed.
Participants	Hospital-based study, Australia. 41 patients (41 men), age range 27-77 years, with primary osteoporosis. Inclusion criterion: at least one fragility fracture. Disease exclusions: disease known to affect bone or mineral metabolism, normal 25(OH) vitamin D and bone mineral density T score values. Drug exclusions: none given.
Interventions	1. Calcitriol 0.5 mcg twice daily and calcium placebo twice daily. Randomised 21, completed 17. 2. Calcium 500 mg twice daily and calcitriol placebo twice daily. No intervention. Randomised 20, completed 16. Duration of treatment 2 years.
Outcomes	Measured over first and second years and overall. 1. Number of persons sustaining new vertebral fracture. 2. Number of persons sustaining new non-vertebral fracture. 3. Numbers of persons with adverse events. 4. Bone mineral density of lumbar spine and femoral neck, total body bone mineral content. 5. Biochemical markers of bone formation and breakdown, PTH, 25(OH) vitamin D, 1,25(OH)2 vitamin D.
Notes	Dr Ebeling provided details of numbers randomised and details of non-vertebral fractures 15/02/2005.

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Falch 1987

Methods	Randomised trial. Evaluation at 3 years by blinded observers. 76 of 86 completed.
Participants	University Hospital, Norway. 62 postmenopausal women aged 50-65 years (mean age 59.6 years) who had sustained a fracture of the distal left forearm. Disease exclusions: if incident fall was from greater than standing height, previous fracture of the right forearm, endocrine disease, malabsorption, gastric surgery, nephrolithiasis, renal failure. Drug exclusions: oestrogens, anticonvulsants, glucocorticoids.
Interventions	1. Calcitriol 0.5 mcg daily (reduced to 0.25 mcg if serum calcium rose above 2.65 mmol/L). Randomised 47, completed 39. 2. Vitamin D3 400 IU daily (Oral). Randomised 39, completed 37. No calcium supplements or manipulation of dietary calcium involved. Duration of treatment 3 years.
Outcomes	Measured at 3 years 1. Number of women sustaining new vertebral fracture. 2. Number of women sustaining new hip fracture. 3. Number of women sustaining other new appendicular fracture. 4. BMC distal radius. 5. BMC proximal radius.
Notes	Additional data provided by Dr Falch by letter on site of appendicular fractures.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Flicker 2005

Methods	Individual remote from institutions undertook randomisation. Double-blind trial. Losses to follow up at 2 years for fracture data of 258 of 693 (37%).
Participants	60 assisted living facilities and 89 nursing homes, Australia. 693 randomised, 625 took medication (594 women, 31 men), mean age 83.4 yr (SD 6.6). Inclusion criterion: 25(OH)vitamin D 25-90 nmol/L. Disease exclusions: 25(OH)vitamin D < 25 nmol/L or > 90 nmol/L, thyrotoxicosis in last 3 years, primary hyperparathyroidism treated in last 3 years, multiple myeloma, Paget's disease of bone, history of malabsorption, active malignancy, other disorders affecting bone and mineral metabolism. Drug exclusions: Warfarin, chronic heparin therapy, vitamin D in previous 3 months, glucocorticoids equivalent to >5 mg prednisolone for > one month in preceding year, current bisphosphonates or hormone replacement therapy.

Flicker 2005 (*Continued*)

Interventions	1. 600 mg calcium as calcium carbonate and 11,000 IU vitamin D 2/week initially then 1000 IU vitamin D2/d. Randomised 346, 313 started supplements, of whom 148 completed 2 years. 2. 600 mg calcium as calcium carbonate and matching vitamin D placebo daily. Randomised 347, 312 started supplements, of whom 146 completed 2 years. Duration of treatment 2 years.
Outcomes	Measured over a follow up of 2 years. 1. Number of persons with any new fracture. 2. Numbers of persons dying.
Notes	Additional data provided by Dr Flicker 07/01/2008

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gallagher 1989

Methods	Two centre double blind randomised placebo-controlled trial. Placebo patients crossed over at 1 year: thus, only 12 month assessment of controlled administration available. Assessors were blinded (two in each centre), inter-observer error calculated for each centre. 58 of 71 completed.
Participants	University Hospital, USA. 58 postmenopausal women mean age 63 years. Sampling technique not described. Osteoporosis defined as one or more non-traumatic vertebral fractures. Disease exclusions: liver or renal disease, any disease known to be associated with disorder of calcium metabolism. Evidence of osteomalacia on biopsy. Drug exclusions: drugs associated with disorders of calcium metabolism.
Interventions	1. Calcitriol 0.25 mcg twice daily, increased to up to 1 mcg daily under discretion of investigator, monitored by serum calcium. Randomised 33, completed 29. 2. Placebo twice daily. Randomised 38, completed 29. All patients followed a free calcium intake during the study. Duration of treatment 1 year.
Outcomes	Measured at one year. 1. Number of women sustaining new vertebral fracture. 2. Total number of new vertebral fractures in each group. 3. Numbers of persons dying.

Gallagher 1989 (*Continued*)

Notes	Further data are reported for a subsequent year in which placebo patients were transferred to the active treatment group.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Gallagher 1990

Methods	Randomised double blind controlled trial. Safety monitoring by weekly serum analysis. Outcome assessors blinded. 40 of 50 completed.
Participants	University Hospital, USA. 50 postmenopausal women aged 50-78 yr (mean 70 yr), with one or more previous non-traumatic vertebral fracture. Recruitment from a referral population. Disease exclusions: renal failure, malignancy, gastro-intestinal abnormalities, parathyroid disease, thyroid disease, acromegaly, Cushings syndrome, arthritis, overt vitamin D deficiency (bone biopsy confirmed), history of renal stones, diabetes or alcoholism. Previous prolonged immobilisation. Drug exclusions: corticosteroids, anti-convulsants, oestrogen or calcium supplements within previous six months or sodium fluoride within one year.
Interventions	1. Calcitriol 0.25 mcg twice daily orally, increased by the investigators at two weekly intervals up to a maximum of 2 mcg per day. Mean dose 0.62 mcg per day. Plus vitamin D2 400 IU daily orally. Calcium intake adjusted to 1 gram daily using calcium supplements if necessary. Randomised 25, completed 18. 2. Placebo plus vitamin D2 400 IU daily orally, plus calcium intake adjusted to 1 gram daily. Randomised 25, completed 22. Duration of treatment 2 years.
Outcomes	Measured at 2 years. 1. Number of women sustaining a new vertebral fracture. 2. Total number of new vertebral fractures in each group. 3. BMD lumbar spine. 4. BMD total body. 5. Total body calcium. 6. Metacarpal index. 7. Bone biopsy. 8. Renal disease.
Notes	See also Aloia 1989, Ott 1989, carried out under same protocol but published separately. Dr Gallagher contacted and provided additional information.

Risk of bias

Gallagher 1990 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gallagher 2001

Methods	Random allocation. No further details. Blinding of outcome assessors reported. 213 of 246 completed.
Participants	Mailing list, United States. 246 women, age range 65-77 yr. Inclusion criterion: femoral neck bone mineral density within 2 standard deviations of the normal range for age. Disease exclusions: severe chronic illness, primary hyperparathyroidism, active renal stone disease. Drug exclusions: bisphosphonates, anticonvulsants, oestrogen, fluoride, thiazide diuretic in last 6 months.
Interventions	1. Calcitriol 0.25 mcg twice daily. Randomised 123, completed 101. 2. Placebo interventions. Randomised 123, completed 112. 3. Conjugated oestrogen 0.625 mg and medroxyprogesterone 2.5 mg daily if intact uterus (group not used here). 4. Calcitriol and hormone replacement therapy (group not used here). Duration of treatment 3 years.
Outcomes	Measured over 3 years. 1. Number of persons sustaining new hip fracture. 2. Number of persons sustaining new non-vertebral fracture. 2. Number of persons sustaining new vertebral fracture. 3. Numbers of persons with adverse events (kidney stone, gastrointestinal). 4. Numbers of persons dying. 5. Bone mineral density of lumbar spine, proximal femur, total body. 6. PTH, 25(OH) and 1,25(OH)2 vitamin D; biochemical markers of bone formation and breakdown.
Notes	Dr JC Gallagher provided extra fracture data 21/02/2005.

how many?

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Garay Lillo 1997

Methods	Divided "randomly". At two years 3910 of 6945 completed.
Participants	Community-based study, Spain. 6945 ambulant community living women between 65 and 85 years of age. Disease exclusions: abnormal renal function (serum creatinine > 144 mcmol/L), serious medical problems, thyroid or parathyroid abnormalities, intestinal malabsorption, previous gastrectomy. Drug exclusions: administration of calcium or vitamin D in the previous six months; administration of corticosteroids, anticonvulsants, or thyroxine in the year prior to enrolment.
Interventions	1. Tricalcium phosphate 1.2 g daily + 25 (OH) vitamin D 16,000 IU per week. Randomised unclear, analysed 2086. 2. Tricalcium phosphate 1.2 g daily. Randomised unclear, analysed 2099. Duration of treatment 2 years.
Outcomes	Measured at one and at two years 1. Number of women sustaining a hip fracture Also measured, but not considered in this review were bone mineral density and biochemical measures.
Notes	Unclear in the published report: details of randomisation Details of losses Details of how fracture outcome was ascertained. Letter sent 10/02/2005

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Geusens 1986

Methods	Randomisation stated but method not defined. Double-blind (triple dummy) design. Radiologic outcome assessor blinded. 34 of 60 completed.
Participants	University Hospital, Belgium. 48 women and 12 men (mean age not reported, but median ages for completed participants 65 yr for group 1; 75 yr for group 3). Inclusion criteria: evidence of vertebral collapse without trauma. Disease exclusions: other diseases that might cause osteoporosis. All had normal thyroid function, serum cortisol profile, serum creatinine, phosphate, calcium, PTH. Biochemical and radiological signs of osteomalacia were absent.

Geusens 1986 (*Continued*)

Interventions	1. Nandrolone decanoate (deca-durabolin)50 mg every 3 weeks. Randomised ?20, completed 11. 2. 1-alpha-hydroxy vitamin D3 1 mcg daily orally. Randomised ?20, completed 11. 3. Elemental calcium 15 mg (as calcium gluconate)per kg body weight by IV infusion, daily for 12 days. Randomised ?20, completed 12. Duration of treatment 2 years. Each active agent accompanied by double dummy placebo.
Outcomes	Measured at 2 years. 1. Metacarpal cortical thickness and fractional cortical thickness. 2. BMC radius. 3. Number of patients with new fractures. 4. Number of new fractures. 5. Biochemical measures: serum calcium, protein, alkaline phosphatase, creatinine, urinary calcium, creatinine, hydroxyproline.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Gorai 1999

Methods	Random allocation. List of randomly generated treatment codes prepared by one of the investigators. No blinding of outcome assessors reported. Unclear how many from 44 completed.
Participants	Outpatient study, Japan. 44 patients women, average age 51 years. Inclusion criteria: postmenopausal women at least one year but not more than 5 years since last menses. Disease exclusions: surgical menopause, chronic disease (renal disease, hyperparathyroidism, diabetes mellitus), compression fracture on thoracic or lumbar spine radiograph. Drug exclusions: drug treatment known to affect bone metabolism.
Interventions	1. 1 mcg 1alpha-hydroxyvitamin D3 daily. Randomised 20, completed unclear. 2. No intervention. Randomised 24, completed unclear. 3. 1 mcg 1alpha-hydroxyvitamin D3 and 0.625 mg conjugated oestrogen daily (group not used here). 4. 0.625 mg conjugated oestrogen daily (group not used here). Duration of treatment 2 years.

Gorai 1999 (*Continued*)

Outcomes	Measured at two years. 1. Number of persons sustaining new vertebral fracture. 2. Numbers of persons with hypercalcaemia. 3. Bone mineral density of lumbar spine and femoral neck. 4. Biochemical markers of bone formation and breakdown.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Harwood 2004

Methods	Random allocation. Computer-generated random number lists and opaque, sealed envelopes. Blinding of outcome assessors stated. 119 of 150 completed.
Participants	Community-based study, United Kingdom. 150 women, mean age 81.2 years on fast-tract orthogeriatric rehabilitation ward. Inclusion criteria: within 7 days of surgery for hip fracture, community residence and independent in activities of daily living. Disease exclusions: institutionalised, diseases know to affect bone metabolism, abbreviated mental test score < 7 at time of recruitment. Drug exclusions: medications know to affect bone metabolism.
Interventions	1. Vitamin D2 300,000 IU by injection once at beginning of trial. Randomised 38, completed 30. 2. Vitamin D2 300,000 IU by injection once at beginning of trial and calcium 1000 mg daily as two tablets. Randomised 36, completed 25. 3. Vitamin D3 800 IU and calcium 1000 mg daily as two tablets. Randomised 39, completed 29. 4. No trial treatment. Randomised 37, completed 35. Duration of treatment 1 year.
Outcomes	Measured over follow up of one year. 1. Number of persons sustaining new non-vertebral fracture. 2. Number of persons sustaining hew hip fracture. 3. Numbers of persons dying. 4. Numbers of persons developing hypercalcaemia. 5. Bone mineral density of lumbar spine and proximal femur. 6. PTH, 1,25(OH)2 and 25(OH)vitamin D3.

Harwood 2004 (*Continued*)

Notes	Dr R Harwood provided further details of fractures and deaths 24/01/2003.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Inkovaara 1983

Methods	Quasi-randomised by date of birth. Double-blind placebo-controlled trial, blinding of outcome assessors not described. Losses: none described.
Participants	Community-based study, Finland. 270 women and 57 men living in a municipal home for the aged. Mean 79.5 SD 7.1 years. Exclusions: functional disorders of kidneys (serum creatinine > 150 mcmol/L) or liver (AAT > 40 IU/L or APT > 280 IU/L, hypercalcaemia (serum Ca 2.80 mmol/L) or kidney stones.
Interventions	1. Calcium plus vitamin D3 daily with placebo. Randomised 46 completed 30. 2. Vitamin D3 1000 IU daily with double placebo. Randomised 45 completed 32. 3. Elemental calcium 1.2 g daily, with double placebo. Randomised 42 completed 31. 4. Placebo. Randomised 42 completed 28. 4 additional groups had methanedione alone or in combination: they are not analysed here. Duration of treatment 9 months.
Outcomes	Measured at 1 year 1. Fractures of vertebrae or wrist (assessed in a sample N = 10 in each group). 2. Hypercalcaemia. 3. Numbers of persons dying. 4. Body weight. 5. Serum biochemistry: calcium, phosphate, creatinine, alkaline phosphatase, aspartate aminotransferase.
Notes	Unclear whether the data represent fractures or participants with fractures. Data have not been included in the appropriate meta-analyses.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ishida 2004

Methods	Random allocation. No further details. Blinding of outcome assessors reported. 123 from 132 completed.
Participants	Outpatient study, Japan. 132 women, age range 50-75 years. Inclusion criteria: at least 5 years since natural or surgical menopause, one or more vertebral fractures (T4 - L4) and bone mineral density of distal third of radius 20% below the mean for young adults (or 30% below the mean for young adults if no fracture). Disease exclusions: recent cancer, another metabolic bone disease, important abnormality in routine blood tests, history of bilateral hip fractures, any physical or mental condition precluding participation. Drug exclusions: recent drug treatment known to affect bone.
Interventions	1. 1alpha-hydroxyvitamin D3 1 mcg/day. Randomised 66, 63 completed. 2. No intervention. Randomised 66, 60 completed. 3. Conjugated oestrogen 0.625 mg and medroxyprogesterone 2.5 mg daily (group not used here). 4. Etidronate 200 mg daily followed by 10-week medication-free periods (group not used here). 5. Eel calcitonin 20 IU/week (group not used here). 6. Vitamin K (menatetrenone)45 mg daily (group not used here). Duration of treatment 2 years.
Outcomes	Measured at two years. 1. Number of persons sustaining new non-vertebral fracture 2. Number of persons sustaining new vertebral fracture. 3. Number of persons sustaining new hip fracture. 4. Numbers of persons with adverse events. 5. Bone mineral density of distal third of the radius. 6. Biochemical markers of bone formation and breakdown.
Notes	Dr Y Ishida provided further information on publications 21/02/2005

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Komulainen 1998

Methods	Randomised open controlled trial, factorial design. Randomisation in blocks of 4, 8 or 12. 226 of 232 completed (of groups used here).
Participants	Community-based study, Finland. 464 whose last menstrual period was 6-24 months previously (mean age 52.7 yr). Exclusion criteria: contraindications for HRT, history of breast or endometrial cancer, thromboembolic diseases, and medication resistant hypertension.

Komulainen 1998 (*Continued*)

Interventions	1. HRT. Sequential combination of 2 mg estradiol valerate days 1 to 21, and 1 mg cyproterone acetate days 12 to 21, treatment free interval days 22 to 28 (group not used here). 2. Vitamin D3 (cholecalciferol)300 IU + calcium lactate 500 mg per day, no intake during June to August each year. Randomised 116, completed 113 at 5 years. 3. Treatments 1) and 2) combined (group not used here). 4. "Placebo" (calcium lactate 500 mg daily - 93 mg elemental calcium). Randomised 116, completed 113 at 5 years. Duration of treatment 5 years.
Outcomes	Measured at five years. 1. Number of women with a first non-vertebral. fracture during five years. 2. Number of fractures. 3. Number of persons dying. Fractures were secondary outcomes in this study, which was powered for detection of changes in bone mineral density. Also measured, but not considered in this review were bone mineral density and biochemical measures.
Notes	Author provided mortality data 11/11/2004.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Law 2006

Methods	Cluster randomisation by computer, no further details. Blinding of outcome assessors not stated. Losses to follow up at mean or median of 10 months for fracture data of 113 of 3717 (3%).
Participants	Clusters of participants in 30 bedded units in care homes or entire care home if small, United Kingdom. 3717 patients (2825 women, 892 men), mean age 85 years. Inclusion criteria: 60 years and over, not temporary residents. Drug exclusions: sarcoidosis, malignancy, life-threatening illness. Drug exclusions: already taking calcium/vitamin D or drugs increasing bone density.
Interventions	1. Ergocalciferol (vitamin D2) 2.5 mg every 3 months (1100 IU/d) Randomised 1762, completed 1366. 2. No treatment. Randomised 1955, completed 1569. Mean or median duration of treatment 10 months (interquartile range 7-14 months).
Outcomes	Measured over a follow up of mean or median of 10 months. 1. Number of persons sustaining new hip fracture. 2. Number of persons sustaining new non-vertebral fracture.

Law 2006 (*Continued*)

	3. Number of persons with hypercalcaemia. 4. Numbers of persons dying. 5. 25(OH)D and PTH in subgroup of 18 participants.
Notes	In the case of meta-analyses including the cluster randomised trial by Law 2006, adjustments to the number of participants with outcomes and denominators in Law 2006 were made using an intraclass correlation coefficient of 0.026. Publication reports analysis taking into account cluster randomisation.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Lips 1996

Methods	Double blind, block randomisation. 1626 of 2578 completed.
Participants	Community-based study, Netherlands. 2578 elderly people (1916 women and 662 men) 70 years and older (mean age 80 SD 6 years) recruited from general practitioners, and from apartment houses and homes for the elderly in the vicinity of Amsterdam, Netherlands. Inclusion criterion: reasonably healthy. Exclusions: history of hip arthroplasty, known hypercalcaemia, history of hip fracture.
Interventions	1. Vitamin D3 400 IU daily in a single tablet. Randomised 1291, completed 834. 2. Identical placebo daily as a single tablet. Randomised 1287, completed 792. All participants received written advice on dairy consumption aimed at assuring a calcium intake of 800-1000 mg/day. Duration of treatment initially 3 years but to attain numbers some participants continued for 3.5 years.
Outcomes	Measured at 3 years. 1. Hip fracture. 2. Other appendicular skeleton fracture. 3. Serum 25(OH)D concentrations (sample only). 4. Hip BMD (non-random subsample). 5. Number of persons dying.
Notes	

Risk of bias

Item	Authors' judgement	Description

Lips 1996 (*Continued*)

Allocation concealment?	Yes	A - Adequate

Lyons 2007

Methods	Double-blind randomised trial with secure allocation at remote site. Losses to follow up at 3 years for fracture data of 1606 of 3440 (47%).
Participants	Residential homes (38%), nursing or dual-registered home (55%), sheltered accommodation (7%), Wales. 3440 participants (2624 women, 816 men), mean age 84 years. Inclusion criteria: resident in participating residential or nursing homes/sheltered housing; regardless of cognitive, visual, hearing or communication impairment. Disease exclusions: taking 400 IU or more vitamin D/d or known contraindication to vitamin D. Drug exclusions:
Interventions	1. Ergocalciferol (vitamin D2) 2.5 mg (100,000 IU) every 4 months as two tablets (822 IU/d). Randomised 1725, completed unclear. 2. Two matching placebo tablets every 4 months. Randomised 1715, completed unclear. Duration of treatment 3 years.
Outcomes	Measured over a follow up of 3 years. 1. Number of persons sustaining new hip fracture. 2. Number of persons sustaining new non-vertebral fracture. 3. Number of persons sustaining new vertebral fracture. 4. Numbers of persons dying. 5. 25(OH)D and PTH in subgroup of 102 participants.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Menczel 1994

Methods	Randomised double blind study. 46 of 66 completed.
Participants	University and tertiary institutions, Israel. 66 osteoporotic postmenopausal women, mean age 67 years. Inclusion based on interpretation of lateral spine radiographs. Exclusion criteria: medical condition or medication known to affect bone metabolism (including HRT), a history of recent kidney stones, creatine clearance less than 50 ml/min/1.73 m2, serum calcium above 10.8 mg/dl.

Menczel 1994 (*Continued*)

Interventions	1. 1- alpha-OH D3 0.25 mcg plus calcium 500 mg, twice daily. Randomised 24, completed 17. 2. Placebo plus calcium 500 mg twice daily. Randomised 42, completed 29. Duration of treatment 3 years.
Outcomes	Measured at three years. 1. New vertebral fractures. 2. Radial styloid BMC (SPA). 3. Serum Ca, PO4. 4. Creatinine clearance. 5. Urinary calcium. 6. Clinical side effects (gastro-intestinal).
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Meyer 2002

Methods	Quasi-randomised. Random allocation based on date of birth. Blinding of patients, nursing staff and study investigators stated. 715 of 1144 completed at 24 months.
Participants	Nursing homes, Norway. 1144 patients (868 women, 276 men), mean age 84.7 years. Inclusion criteria: life expectancy > 6 months, not permanently bedridden, not having difficulties taking medicine. Disease exclusion: none given. Drug exclusions: vitamin D supplementation of > 10 mcg/day.
Interventions	1. Cod liver oil 5 ml with vitamin D3 2.2 mcg/ml. Randomised 569, completed 366. 2. Cod liver oil 5 ml with vitamin D3 0.1 to 0.2 mcg/ml (control). Randomised 575, completed 349. Duration of treatment 2 years.
Outcomes	Measured over 24 months. 1. Number of persons sustaining new hip fracture. 2. Number of persons sustaining new non-vertebral fracture. 3. Numbers of persons dying.
Notes	

Meyer 2002 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

Nuti 2006

Methods	Random allocation, no further details. Double-blind trial. Losses to follow up at 18 months for fracture data of 51 of 148 (34%).
Participants	11 clinical centres, Italy. 148 patients (all women), mean age 64 years (N = 136). Inclusion criteria: 55-75 yr, at least 5 yr after menopause, one prior vertebral fracture on x-ray and/or lumbar or femoral bone mineral density T-score < -2.5. Disease exclusions: secondary osteoporosis, other bone diseases, significant concomitant disease, hypercalcaemia, hypercalciuria, serum 25(OH)D3 < 25 nmol/L by high performance liquid chromatography. Drug exclusions: drugs influencing bone (oestrogens, progesterone), selective estrogen receptor modulators, calcitonins, vitamin D and calcium for more than one month in last 3 months, bisphosphonates, fluoride, ipriflavone, glucocorticoids, immunosuppressives, anticonvulsants, lithium for more than one month in last 6 months.
Interventions	1. Alfacalcidol D3 1 mcg tablet/day plus placebo. Randomised 76, 50 completed at 18 months for fracture assessment. 2. 880 IU vitamin D3 and 1000 mg calcium/d (as calcium carbonate)placebo. Randomised 72, 47 completed at 18 months for fracture assessment. Duration of treatment 18 months.
Outcomes	Measured over a follow up of 18 months. 1. Number of persons with new vertebral fracture. 2. Number of persons with gastrointestinal adverse events, renal stones.
Notes	

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Orimo 1994

Methods	Multicentre, randomised double blind placebo controlled trial. By implication, and the address of the "controller" allocation concealment appears adequate. A thorough analysis of withdrawal and exclusion is presented. 53 of 80 completed at 1 year. Analysis by intention to treat not provided.
Participants	University and community hospitals, Japan. 80 postmenopausal women aged 65 yr or older, mean age 71 yr. Inclusion criteria: established osteoporosis, defined as decreased bone mass, presence of fractures of spine, femoral neck, or radius, with normal levels of serum calcium, phosphate or alkaline phosphatase. Disease exclusions: hypercalcaemia, osteomalacia, primary/secondary hyperparathyroidism, rheumatoid arthritis, bone metastases, multiple myeloma, secondary osteoporosis, history of prolonged immobilisation. Drug exclusions: any of the following in the previous two months: oestrogen, progesterone, androgen, calcitonin, bisphosphonate, vitamin D metabolites or analogues, ipriflavone, vitamin K2, corticosteroids, or anticonvulsants.
Interventions	1. 1-alpha-OH D3 1 mcg, plus elemental calcium 300 mg (as calcium lactate) daily. Randomised 38, completed 25. 2. Identical placebo, plus elemental calcium 300 mg daily. Randomised 42, completed 28. Duration of treatment 1 year.
Outcomes	Measured at one year. 1. Number of new vertebral fractures. 2. New vertebral fracture rate. 3. Lumbar spine BMD (L2-L4) measured by DEXA. 4. Femoral neck BMD. 5. Biochemical measures, including hypercalcaemia.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Ott 1989

Methods	Double blind randomised controlled trial. 72 of 86 completed.
Participants	Tertiary hospital, USA. 86 women with post menopausal osteoporosis aged 50 to 80 (mean age 67.5 yr). Inclusion criterion: at least one non-traumatic vertebral compression fracture. Disease exclusions: hepatic or renal disease, malignancy, malabsorption, parathyroid or thyroid disorder, inflammatory arthritis, alcoholism, overt vitamin D deficiency, history of renal stones, insulin dependent diabetes, previous long term hospitalisation, any other disorder known to affect bone metabolism.

Ott 1989 (*Continued*)

	Drug exclusions: glucocorticoids, anticonvulsants, oestrogens, sodium fluoride, calcium supplements, pharmacologic doses of vitamin D.
Interventions	1. Calcitriol (1,25 OH2 D3) 0.25 to 2.00 mcg daily (0.25 mcg capsules), physician adjusted depending upon serum and urinary calcium levels. Randomised 43, completed 35. 2. Placebo. Number of capsules adjusted as in 1. Randomised 43, completed 37. All women had supplement if necessary to bring calcium intake to 1000 mg per day. Duration of treatment 2 years.
Outcomes	Measured at two years. 1. Number of persons sustaining new vertebral fractures. 2. Number of persons sustaining hip fractures. 3. Number of persons sustaining other appendicular skeleton fractures. 4. BMC radius (33 outcomes at 2 years). 5. BMD spine (33 outcomes at 2 years). 6. Total body calcium (neutron activation analysis) (28 outcomes at 2 years). 7. Hypercalcaemia.
Notes	See also Aloia 1988 and Gallagher 1990 for separate reports from other participating centres.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Peacock 2000

Methods	Double-blind placebo-controlled trial, blinding of outcome assessors not described. Losses: none described.
Participants	Community study, USA. 438 (316 women, 122 men), mean age women 74 years, men 76 years. Inclusion criteria: willing to undertake 4 year study, aged 60 yr or over, able to give informed consent as assessed by Short Portable Mental Status Test. Disease exclusions: terminal illness, Paget's disease, recurrent urinary stone disease, renal disease requiring specific treatment, excluded by primary physician. Drug exclusions: treated with sodium fluoride, bisphosphonates, steroids, dilantin.
Interventions	1. 25(OH) vitamin D3 5 mcg three times daily 2. 250 mg calcium tablet three times daily. 3. Placebo three times daily. Randomised unclear, completed unclear. 2. Calcium 250 mg as calcium citrate malate three times daily, vitamin D placebos three times daily. Randomised unclear, completed unclear. 3. Matched placebo tablets daily. Randomised unclear, completed unclear.

Peacock 2000 (*Continued*)

	Duration of treatment 4 years.
Outcomes	Measured over a follow up of four years. 1. Number of persons sustaining new vertebral fracture. 2. Number of persons sustaining new non-vertebral fracture. 3. Numbers of persons developing hypercalcaemia. 4. Number of persons dying. 5. Number of persons reporting gastrointestinal disorders. 6. Number of people with renal stones. 7. PTH, 25(OH) and 1,25(OH)2 vitamin D. 8. Markers of bone formation and resorption. 9. Femoral neck bone mineral density.
Notes	Emailed Dr Peacock for further details on denominators and outcomes 18/2/2005.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Pfeifer 2000

Methods	Double blind randomised controlled trial. 137 of 148 completed.
Participants	Osteology Clinic, Germany. 148 healthy ambulatory community living women aged 70 years or older, recruited through advertisement. Inclusion criteria: 25-hydroxycholecalciferol serum level below 50 nmol/litre, not holidaying at a different latitude. Disease exclusions: hypercalcaemia, primary hyperparathyroidism, osteoporotic extremity fracture, intolerance to vitamin D or calcium; chronic renal failure; drug, alcohol, caffeine, or nicotine abuse; diabetes mellitus. Drug exclusions: treatment with bisphosphonate, calcitonin, vitamin D or metabolites, oestrogen, tamoxifen in past 6 months; fluoride in last 2 years; anticonvulsants or medications possibly interfering with postural stability or balance.
Interventions	1. Elemental calcium (calcium carbonate)600 mg plus vitamin D3 400 IU. Randomised 74, completed 70. 2. Calcium carbonate 600 mg. Randomised 74, completed 67. Supplementation at the end of winter for 8 weeks.
Outcomes	Measured at one year. 1. The number of persons sustaining non-vertebral fracture. 2. The number of persons sustaining a fall (not part of this review). 3. Number of falls in each group (not part of this review). Also measured, but not considered in this review were body sway parameters, and biochemical measures.

Pfeifer 2000 (*Continued*)

Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Porthouse 2005

Methods	Random allocation, initially 2:1 ratio intervention to control. Remote site computer randomisation. Blinding of outcome assessors not stated. 3199 of 3314 completed.
Participants	Multicentre general practice study, United Kingdom. 3314 patients (all women), mean age 77 years, with at least one self-reported risk factor for hip fracture. Inclusion criteria: low body weight (< 58 kg), personal history of fracture, maternal history of hip fracture, current smoker, poor or fair health. Disease exclusions: kidney or bladder stones, renal failure, hypercalcaemia, cognitive impairment, life expectancy < 6 months. Drug exclusions: current calcium supplementation of > 500 mg/day.
Interventions	1. Calcium 1000 mg and vitamin D3 800 IU given as two tablets daily, nurse gave general lifestyle advice, and information leaflet on calcium and vitamin D and on falls prevention. Randomised 1321, completed 1269. 2. Information leaflet on calcium and vitamin D and on falls prevention. No intervention. Randomised 1993, completed 1930. Duration of treatment 18 to 42 months.
Outcomes	Measured over a median follow up of 25 months (range 18 to 42 months). 1. Number of persons sustaining new hip fracture. 2. Number of persons sustaining new non-vertebral fracture. 3. Number of persons dying.
Notes	Prof DJ Torgerson provided pre-publication report and further details 09-16/02/2005

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Prince 2008

Methods	Double blind randomised controlled trial. Remote site randomisation. 275 of 302 completed.
Participants	Community-based study, Australia. 302 participants (all women), mean age 77 years. Inclusion criteria: aged 70-90 years, sustained a fall in last 12 months, ambulant, 25(OH)vitamin D < 60 nmol/L. Disease exclusions: hip Z score < -2.0, medical conditions influencing bone metabolism, creatinine > twice reference range, fracture in past 6 months, MMSE < 24, marked neurological conditions likely to substantially impair balance or physical activity, e.g. stroke, Parkinson's disease. Drug exclusions: current consumption of vitamin D or bone active agents.
Interventions	1. Calcium 1000 mg (as calcium citrate two tablets twice daily) and vitamin D2 1000 IU daily. Randomised 151, completed 136. 2. Calcium 1000 mg (as calcium citrate two tablets twice daily) and placebo daily. Randomised 151, completed 139. Duration of treatment one year.
Outcomes	Measured at on year. 1. Number of persons sustaining any fracture. 2. Numbers of persons with hypercalcaemia, gastrointestinal events. 3. Number of persons dying.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

RECORD 2005

Methods	Random allocation. Remote site computer randomisation. Blinding of outcome assessors stated. Losses to follow up at 24 months for fracture data of 58 of 5292 (1%).
Participants	Community-based study, United Kingdom. 5292 patients (4481 women, 811 men), mean age 77 years. Inclusion criteria: osteoporotic fracture within the last ten years, aged 70 years or over. Disease exclusions: bed or chair bound prior to fracture, cognitive impairment indicated by an abbreviated mental test score of under seven, suffered from cancer likely to metastasise to bone within the previous ten years, fracture associated with pre-existing local bone abnormality, known hypercalcaemia, renal stone in the last 10 years, life expectancy less than six months, known to be leaving the UK. Drug exclusions: taking more than 200 IU (5 mcg) vitamin D or more than 500 mg calcium supplements daily; had fluoride, bisphosphonates, calcitonin, tibolone, hormone replacement therapy, selective estrogen

RECORD 2005 (*Continued*)

	receptor modulators, or any vitamin D metabolite (such as calcitriol)in the last 5 years; vitamin D by injection in the last year.
Interventions	1. Calcium 1000 mg and vitamin D3 800 IU given as two tablets daily. Randomised 1306, completed 921 at 24 months (questionnaires and tablets). 2. Calcium 1000 mg given as two tablets daily. Randomised 1343, completed 993 at 24 months (questionnaires and tablets). 3. Vitamin D3 800 IU given as two tablets daily. Randomised 1311, completed 905 at 24 months (questionnaires and tablets). 4. Two placebo tablets daily. Randomised 1332, completed 946 at 24 months (questionnaires and tablets). Duration of treatment 24 to 62 months.
Outcomes	Measured over a follow up of 24 to 62 months. 1. Number of persons sustaining new hip fracture. 2. Number of persons sustaining new non-vertebral fracture. 3. Number of persons with new clinical vertebral fracture. 4. Number of persons with hypercalcaemia, renal stone or failure, gastrointestinal adverse events. 5. Numbers of persons dying. 6. 25(OH)D3 and PTH (subgroup of 60 participants).
Notes	Prof AM Grant provided pre-publication report

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Sato 1997

Methods	Double-blind randomised study. 64 of 84 completed.
Participants	University Hospital, Japan. 84 hospital outpatients who had hemiplegia after stroke. Analysis based on 64 completing participants, (35 men, 29 women) of mean age 68.5 yr. Disease exclusions: shoulder-hand syndrome, multiple strokes, history of hip fracture, stroke duration of less than one month. Drug exclusions: use of estrogen, calcium, vitamin D, corticosteroids, thyroxine, or anticonvulsants.
Interventions	1. 1-alpha-hydroxy vitamin D3 1.0 mcg daily. Randomised 45, completed 30. 2. Identical placebo. Randomised 39, 34 completed. Both groups received 300 mg calcium daily. Duration of treatment 6 months.

Sato 1997 (*Continued*)

Outcomes	Measured at six months. 1. Number of participants sustaining a hip fracture. Also measured, but not considered in this review were bone mineral density, and biochemical measures.
Notes	Emailed Dr Sato 14/10/2005 asking for further details of deaths during the study.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Sato 1999a

Methods	Double-blind randomised study. Losses: none described.
Participants	University Hospital, Japan 86 (35 men, 51 women) elderly people with Parkinson's disease, mean age 70.6 years. Disease exclusions: history of previous non-vertebral fracture, non-ambulatory (Hoehn and Yahr Stage 5 disease), hyperparathyroidism, renal osteodystrophy, impaired renal, cardiac or thyroid function. Drug exclusions: therapy with corticosteroids, estrogens, calcitonin, etidronate, calcium, or vitamin D at any time in the previous 2 months, or for more than 3 months out of the previous 18.
Interventions	1. 1-alpha-hydroxy vitamin D3 1.0 mcg daily. 2. Identical placebo. Duration of treatment 18 months.
Outcomes	Measured at 18 months 1. Number of participants sustaining a fall associated hip fracture. 2. Other fall-associated non-vertebral fractures. 3. Number of self-reported falls per subject (not part of this review). Also measured, but not considered in this review were bone mineral density, and biochemical measures.
Notes	Required: details of randomisation, falls data. Letter sent 14/10/2004 asking for details of reported deaths in trial.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Sato 1999b

Methods	No blinding reported. 60 of 69 completed.
Participants	Outpatient study, Japan. 69 patients (39 women, 30 men), average age 71 years. Inclusion criteria: post-stroke hemiplegia, at least one year post-stroke. Disease exclusions: congestive heart failure, obstructive pulmonary disease, other known causes of osteoporosis (hyperparathyroidism, renal osteodystrophy), impairment of renal, cardiac, or thyroid function. Drug exclusions: corticosteroids, oestrogen, calcitonin, etidronate, calcium or vitamin D3 for 3 months or longer in 12 months before study; or any of these in 2 months preceding study.
Interventions	1. alpha-hydroxyvitamin D3 daily 1 mcg. Randomised 34, completed 31. 2. No tablets. No intervention. Randomised 35, completed 29. 3. Ipriflavone 600 mg daily (group not used here). Randomised 34, completed 28. Duration of treatment 1 year.
Outcomes	Measured at one year. 1. Number of persons sustaining new hip fracture. 2. Numbers of persons with adverse events. 3. Bone mineral density of second metacarpal. 4. Biochemical markers of bone formation and breakdown, PTH, 25(OH) vitamin D, 1,25(OH)2 vitamin D.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Shiraki 1996

Methods	Multi-centre, randomised, double-blind placebo-controlled study. 79 of 113 completed.
Participants	University and Community Hospitals, Japan. 113 community living osteoporotic women (mean age 72.4 years). Analysis based on 79 completing participants mean age 71.4 years). Inclusion criteria: aged 60 years and over, osteoporotic. Disease exclusions: presence of disease affecting bone or calcium metabolism, abnormal liver or kidney function. Drug exclusions: any treatment for osteoporosis during the previous six months.
Interventions	1. 1-alpha-hydroxy vitamin D3 0.75 mcg daily. Randomised 113, completed 79. 2. Identical placebo.

Shiraki 1996 (*Continued*)

	Participants in each group were given calcium lactate 2.3 g daily (300 mg elemental calcium). Duration of treatment 2 years.
Outcomes	Measured at two years. 1. Number of participants sustaining a radiographic vertebral fracture (diagnosed if anterior or central vertebral height was 20% less than the posterior height).
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Smith 2007

Methods	Double-blind random allocation to previously randomised, consecutive ampoules, identical in appearance. Blinding of outcome assessors stated. Losses: 259 of 4570 at 36 months.
Participants	Multicentre general practice study in 111 sites, United Kingdom. 9440 patients (4354 women, 5086 men), median age 79.1 years. Inclusion criteria: aged 75 years and older, consenting and presenting for influenza vaccination at general practice. Disease exclusions: history of renal failure, renal stones, hypercalcaemia, sarcoidosis, current cancer, bilateral hip replacement, any history of treated osteoporosis. Drug exclusions: taking 10 mcg or more vitamin D daily.
Interventions	1. Intramuscular vitamin D (ergocalciferol)300,000 IU annually every autumn. 2. Identical placebo. Duration of treatment 3 years (annual injections), recruited in annual waves. Randomised 9440, 3 year data for 4570.
Outcomes	Measured over follow up of three years. 1. Number of persons sustaining new hip fracture. 2. Number of persons sustaining new non-vertebral fracture. 3. PTH, 25(OH)vitamin D, 1,25(OH)2 vitamin D.
Notes	Prof C Cooper and Dr S Crozier provided further details 23/02/2005.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Tilyard 1992

Methods	Multi-centre randomised single blind comparison of calcitriol and calcium supplementation. No placebo, and each participating physician (123) had own separate randomisation code. Participant compliance not checked. 515 of 622 completed at one year, 476 at two years, 432 at three years.
Participants	Community-based study, New Zealand. 622 fully ambulatory post-menopausal women aged 50 to 79 yr, (mean 63.7 yr) with no evidence of disease or drug known to cause osteoporosis, from a population referred with fracture or other manifestation of effects of osteoporosis. Inclusion criteria: presence of one or more non-traumatic vertebral compression fracture seen on a lateral spinal radiograph. Exclusion criteria: not specifically described.
Interventions	1. Calcitriol 0.5 mcg daily in 2 doses by mouth. Randomised 314, completed 1 yr 262, 2 yr 236, 3 yr 213. 2. Elemental calcium 1 g daily (5.2 g calcium gluconate twice daily.) Randomised 308, completed 1 yr 253, 2 yr 240, 3 yr 219. Patients instructed not to take any other calcium supplement, but otherwise diet, and exercise programmes were unsupervised. Duration of treatment 3 years.
Outcomes	Measured at one, two, and three years. 1. Number of women with new vertebral fractures. 2. Number of fractures of the appendicular skeleton by the end of three years of treatment. 3. Episodes of hypercalcaemia. 4. Renal calculi. 5. Number of persons dying. 6. Gastro-intestinal symptoms.
Notes	Interim reports published in 1990 and 1991.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Trivedi 2003

Methods	Participants and investigators blinded until study ended, when pharmacy revealed coding. 2055 of 2686 available for intention to treat at 5 years.
Participants	Community-based study, UK. 2686 (2037 men and 649 women) mean 75 yr, from register of British doctors and register of a general practice. Inclusion criteria: age 65-85 years, living in the community, from British doctors study register and general practice register in Ipswich. Disease exclusions: contraindications to vitamin D supplementation e.g. renal stones, sarcoidosis, malig-

Trivedi 2003 (*Continued*)

	nancy. Drug exclusions: already taking vitamin D supplements.
Interventions	1. Vitamin D3 (cholecalciferol)100,000 IU. Randomised 1345, completed 1038. 2. Placebo: one capsule four monthly. Randomised 1341, completed 1017. Duration of treatment 5 years.
Outcomes	1. Non-vertebral fractures at 5 years. 2. Hip fractures at 5 years. 3. Vertebral fractures at 5 years. 4. Falls. 5. Self-reported health. 6. In a subgroup, 238 had measurement of PTH, 25-hydroxy vitamin D and heel ultrasound at 4 years. 7. Compliance with trial medication. 8. Adverse effects: death, death from cardiovascular disease, death from cancer.
Notes	Discrepancy between text and table 5 in subgroup study (235 and 238 respectively).

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Ushiroyama 2001

Methods	Random allocation, no further details. No mention of blinding of outcome assessors. No details of loss to follow up.
Participants	Hospital outpatient-based study, Japan. 102 patients (all women), age range 53-58 yr, with osteoporosis/osteopenia. Inclusion criteria: six months or more since last menses, status confirmed by oestradiol and gonadotrophin measurements. Disease exclusions: renal failure, metabolic bone disease, urolithiasis. Drug exclusions: hormonal contraception or postmenopausal oestrogen.
Interventions	1. 1alpha-hydroxy cholecalciferol 0.5 mcg orally twice daily. Randomised 50, number completed unclear. 2. No intervention. Randomised 52, number completed unclear. 3. Calcitonin 10 IU twice a month (group not used here). 4. Calcitonin and 1alpha-hydroxycholecalciferol (group not used here). Duration of treatment 2 years.

Ushiroyama 2001 (*Continued*)

Outcomes	Measured at one year 1. Number of persons sustaining new non-vertebral fracture. 2. Number of persons with hypercalcaemia. 3. Vertebral bone mineral density. 4. PTH, markers of bone formation and resorption.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

WHI 2006

Methods	Double-blind trial. No details on method of randomisation. Losses to follow up at 7 years for fracture data of 2531 of 36282 (7%).
Participants	Community based women, USA. 36282 participants (all women), mean age 62.4 (SD 7.0) years. Inclusion criteria: 50-79 years, no medical condition associated with predicted survival of less than 3 years. Disease exclusions: hypercalcaemia, renal calculi. Drug exclusions: corticosteroid use, calcitriol use, calcium supplements > 1000 mg/d, vitamin D > 600 IU/d (>1000 IU/d after 1999).
Interventions	1. 1000 mg calcium as calcium carbonate and 400 IU vitamin D3 as two tablets daily. Randomised 18176, 93% completed 7 (SD 1.4) years. 2. Two placebo tablets daily Randomised 18106, 93% completed 7 (SD 1.4) years. Duration of treatment 7(SD 1.4) years.
Outcomes	Measured over a follow up of 12 weeks. 1. Number of persons with new hip fracture. 2. Numbers of persons with new clinical vertebral fracture. 3. Numbers of persons with all new fractures (excluding rib, sternum, skull, face, finger, toe, cervical vertebral fracture). 4. Number of persons with gastrointestinal adverse events, renal calculi. 5. Numbers of persons dying. 6. Subgroup of 448 had 25(OH)D measured at 2 years.
Notes	

Risk of bias

Item	Authors' judgement	Description

WHI 2006 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

AAT: aspartate aminotransferase
APT: alkaline phosphatase
BMC: bone mineral content
BMD: bone mineral density
Ca: calcium
HRT: hormone replacement therapy
mcmol/L: micromoles per litre
PO4: phosphate
PTH: parathyroid hormone

Characteristics of excluded studies *[ordered by study ID]*

Aguado 2006	RCT. Oral 80,000 IU 25 hydroxyvitamin D three monthly + 1000 mg calcium/d versus oral 800 IU vitamin D3 + 1000 mg calcium/d. No fracture data.
Aloia 2005	RCT. Oral 800 IU vitamin D3 daily + calcium supplements to give intake of 1200-1500 mg/d versus placebo + calcium supplements to give intake of 1200-1500 mg/d. After 2 years vitamin D increased to 2000 IU D3/d for one year. Designed to evaluate effect on bone mineral density, collection of fracture data not described, no fractures reported.
Baeksgaard 1998	RCT. Placebo controlled. Vitamin D plus calcium, and vitamin D plus calcium plus multivitamins. Two patients with incident vertebral fracture during the study were excluded from the analysis. No fracture data.
Binder 1995	RCT. Bolus of 100,000 IU vitamin D3 orally then 50,000 IU/week + 1000 mg calcium/day versus 1000 mg calcium/day. No fracture data.
Binkley 2007	RCT. 8400 IU vitamin D3 weekly versus placebo. No fracture data.
Brazier 2005	RCT. Oral 800 IU vitamin D3/d + 1000 mg calcium/d as two tablets daily versus two placebo tablets/d. No fracture data.
Broe 2007	RCT. 200 IU vitamin D2/d versus 400 IU vitamin D2/d versus 800 IU vitamin D2/ d versus placebo. No fracture data.
Bunout 2006	RCT. Oral 400 IU vitamin D3 + 800 mg calcium/d versus oral 800 mg calcium/d, also randomised to resistance training or control. No fracture data.
Chen 1997	RCT. 150 mg calcium and 0.75 mcg 1alpha hydroxyvitamin D3 versus calcium 150 mg. No fracture data.
Chevalley 1994	RCT. 800 mg calcium (as calcium carbonate or osseino-mineral complex) versus placebo in vitamin D replete participants. Not a trial of vitamin D supplementation.

(*Continued*)

Cooper 2003	RCT. 10,000 IU vitamin D2/week + 1000 mg calcium/day versus 1000 mg calcium/day. No fracture data.
Corless 1985	RCT. 9000 IU vitamin D2 tablets versus placebo. No fracture data.
Daly 2006	RCT. 400 ml/d milk fortified with 1000 mg calcium and 800 IU vitamin D3 versus control. No fracture data.
Dawson-Hughes 1991	RCT. 400 IU vitamin D versus placebo. No fracture data.
Dawson-Hughes 1995	RCT. 400 IU vitamin D and 377 mg calcium/d versus placebo with 377 mg calcium/d. No fracture data.
Deroisy 1998	RCT. Fracture data (not primary outcome). Study of acceptability and effect of formulation of vitamin D with calcium co-supplementation. (1 g calcium and Vitamin D3 800 IU as two tablets a day versus 1.2 g calcium as two sachets a day and 800 IU as two chewable tablets a day)
Deroisy 2002	RCT. Vitamin D 200 IU + calcium 500 mg versus calcium 500 mg. No fracture data.
Dhesi 2004	RCT. Injection of 600,000 IU ergocalciferol versus placebo. No fracture data.
Doetsch 2004	RCT. Vitamin D3 800 IU + 1 g calcium versus placebo. No fracture data.
Francis 1996	RCT. 0.5 mcg alfacalcidol versus up to 160 mg calcium and 1000 IU vitamin D2. No fracture data.
Gallagher 1982	RCT. 0.5 mcg 1,25-dihydroxyvitamin D3 daily versus placebo. No fracture data.
Gloth 1995	RCT. Calcium v calcium + vitamin D variable dose. No fracture data.
Grados 2003	RCT. 400 IU vitamin D + 500 mg calcium versus placebo. No fracture data.
Grady 1991	RCT. 0.5 mcg 1,25dihydroxyvitaminD3 versus placebo. No fracture data.
Hangartner 1985	Quasi randomised RCT. No fracture data.
Harju 1989	RCT. Calcitonin versus 0.5 mcg 1alpha-hydroxyvitamin D versus control. No fracture data.
Heikinheimo 1992	This study has been widely quoted as evidence for effectiveness of single dose vitamin D in fracture prevention. It is an open quasi-randomised trial. As only individuals recruited in the northern autumn and winter were included for practical reasons, allocation was not concealed, being based on month of birth. There was no placebo and enrolment was biased. Follow up varied from 2-5 years but the cumulative analysis of fracture incidence did not include confidence intervals despite the decreasing numbers with longer follow up. This study was therefore excluded from the analysis but is important for raising the hypothesis that this relatively inexpensive, practical method of fracture prevention should be tested more rigorously.
Honkanen 1990	RCT. 1558 mg calcium + 1800 IU vitamin D versus no treatment. No fracture data.

(*Continued*)

Hunter 2000	RCT. 800 IU vitamin D versus placebo. No fracture data.
Itami 1982	RCT. 1-alpha hydroxyvitamin D3 0.75 mcg daily versus placebo for 30 weeks. No fracture data.
Iwamoto 1999	RCT. HRT versus 1(OH)vitamin D3 versus vitamin K2 versus control. No fracture data.
Iwamoto 2000	RCT. One alpha hydroxyvitamin D3 0.75 mcg/day v vitamin K2 versus One alpha hydroxyvitamin D3 0.75 mcg/day and vitamin K versus calcium lactate 2 g/day. No fracture data.
Jensen 1985	RCT which measures overall spinal length but fracture data unavailable.
Jensen 1982	RCT. 1,25(OH)2D3 0.5 mcg and 500 mg calcium versus calcium v HRT and calcium versus calcium, HRT and 1,25(OH)2D3 0.5 mcg. No fracture data.
Johnson 1980	RCT. 2000 IU vitamin D or placebo. No fracture data.
Keane 1998	RCT. Milk fortified with vitamin D versus unfortified milk. No fracture data.
Kenny 2003	RCT comparing 1000 IU/day and 500 mg/day calcium versus placebo and 500 mg/day calcium. No fracture data.
Krieg 1999	RCT comparing 440 IU D3 and 500 mg calcium/day versus no treatment. No fracture data.
Larsen 2004	RCT with 4 clusters. Participants in each of the three treatment clusters received a medication review co-intervention, but the control group received no intervention. The vitamin D and calcium effect cannot be isolated from the effects of the co-interventions, so this study does not meet the pre-defined inclusion criteria.
Latham 2003	RCT. 300,000 IU vitamin D or placebo, with and without exercise programme. No fracture data.
Meier 2004	RCT. 500 IU vitamin D and 500 mg calcium versus control. No fracture data.
Moschonis 2006	RCT. 1200 mg calcium and 300 IU vitamin D3/d supplemented dairy products versus 600 mg/d calcium supplement versus control. No fracture data.
Nordin 1985	RCT. 15,000 IU vitamin D2 weekly versus placebo. No fracture data.
Ongphiphadhanakul 2000	RCT. 0.25 mcg/day calcitriol v 0.50 mcg calcitriol/day versus low dose estrogen v high dose estrogen (all groups received 750 mg calcium/day. No fracture data.
Ooms 1995	RCT. Vitamin D supplementation, placebo controlled, no fracture data (subset of Lips 1996).
Patel 2001	RCT. 800 IU cholecalciferol versus placebo in first year, crossed over for second year. Age range 24 - 70 years. Mean age 47 years, too young for trial of osteoporotic fracture prevention.
Pedrosa 2006	RCT. 150,000 IU vit D3 monthly for 2 months, then 90,000 IU monthly for 4 months + 1000 mg/d calcium versus placebo + 1000 mg/d calcium. No fracture data.

(*Continued*)

Riera 2003	RCT. 1 mcg/d alfacalcidol and 500 mg/d calcium citrate versus placebo and 500 mg/d calcium citrate. No fracture data.
Riis 1986	RCT. 10 mcg 24R,25(OH)2 vitamin D3 daily or placebo. No fracture data.
Shiraki 1985	RCT. 1 mcg 1,24(R) (OH)2 vitamin D3 versus 1 mcg 1, 24(S) (OH)2 vitamin D3, 0.5 mcg 1 alpha-OHD3 versus 1 mcg 1 alpha-OHD3 daily versus control. No fracture data.
Shiraki 2004	RCT. 1 mcg alfacalcidol and 78 mg calcium versus 78 mg calcium. No fracture data.
Son 2001	RCT. Calcium 1000 mg/day versus 0.5 mcg/day alfacalcidol versus placebo. No fracture data.
Sorensen 1977	RCT. 1/2 mcg 1alphahydroxyvitaminD3 and 1000 mg calcium versus placebo and 1000 mg calcium. No fracture data.
Thomsen 1986	RCT. 24R,25-(OH)2D3 versus placebo. No fracture data.
Ushiroyama 1995	RCT. Placebo controlled, intervention 1-alpha-hydroxyvitamin D. No fracture data.
Ushiroyama 2002	RCT. 1alphahydroxycholecalciferol 1 mcg/d v vitamin K versus 1alphahydroxycholecalciferol 1 mcg/d and vitamin K v control. No fracture data.
Zhu 2006	RCT. 500 mg calcium + 1000 IU vitamin D2/d versus 500 mg calcium/d + placebo. No fracture data.

HRT: hormone replacement therapy
RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

ALFA 2006

Methods	Three-year randomised controlled trial.
Participants	Postmenopausal, alendronate-treated, osteopaenic or osteoporotic women in Europe.
Interventions	1 mcg alfacalcidol or placebo daily.
Outcomes	Falls and bone turnover markers.
Notes	Published abstracts only. Possiblility of fractures reported in main report?

Fujita 1989

Methods	Probably randomised controlled trial.
Participants	Unclear, in Japan.
Interventions	Calcitriol or placebo.
Outcomes	Unclear.
Notes	Decision about inclusion awaiting translation from Japanese.

Hayashi 1992

Methods	Multicentre trial, appears quasi-randomised.
Participants	740 men and women with osteoporosis, in Japan.
Interventions	1 mcg alfacalcidol daily or no treatment.
Outcomes	Fractures as vertebral fractures/1000 patient years.
Notes	Require further details from authors.

Johnell 2001

Methods	Unclear if cluster randomised trial.
Participants	2404 women aged over 50 in 174 nursing homes in Sweden.
Interventions	21,000 IU oral vitamin D3/month or no treatment.
Outcomes	Hip fractures, other fractures, deaths.
Notes	Published abstract. Email from Olof Johnell 09/09/2004 to say publication being drafted.

Lappe 2007

Methods	Four-year randomised controlled trial.
Participants	1179 community-dwelling women over aged over 55 in USA.
Interventions	1100 IU vitamin D3 and 1400-1500 mg calcium/day or 1400-1500 mg calcium and vitamin D placebo or double placebos.
Outcomes	Fractures.
Notes	Cancer incidence data published. Email from Joan Lappe 10/09/2007 saying fracture data publication being drafted.

Matsumoto 2005

Methods	One-year randomised controlled trial.
Participants	219 men and women, mean age 67 years, with osteoporosis, in Japan.
Interventions	1 mcg or 0.75 mcg or 0.5 mcg 1alpha, 25-dihydroxy-2beta (3-hydroxypropoxy)vitamin D3 (called ED-71)/day and 200-400 IU vitamin D3 or 200-400 IU vitamin D3 and placebo.
Outcomes	Fractures, hypercalcaemia.
Notes	Further details needed from authors.

Nakatsuka 1997

Methods	Two-year randomised controlled trial.
Participants	33 participants, mean age 78 years, in Japan.
Interventions	Crossover trial of 1 mcg alfacalcidol and calcium or calcium.
Outcomes	Vertebral fractures.
Notes	Awaiting translation from Japanese.

Orimo 1987

Methods	Probably randomised controlled trial, duration unclear.
Participants	86 women, mean age over 70 years, with osteoporosis, in Japan.
Interventions	1 mcg alfacalcidol or 1 mcg alfacalcidol and 1 g calcium or 1 g calcium daily or no treatment.
Outcomes	Fractures as vertebral fractures/1000 patient years.
Notes	Further details required from authors.

Orwoll 1989

Methods	Two-year randomised controlled trial.
Participants	39 women, mean age 69, with severe osteoporosis, in USA.
Interventions	40 mcg 25-OHD and 1200 mg calcium daily or 1200 mg plus placebo daily.
Outcomes	Fractures as vertebral fractures/patient year.

Notes	Further details required from authors.

OSTPRE-FPS 2007

Methods	Three-year randomised controlled trial.
Participants	5553 women aged 65 years or older, in Finland.
Interventions	800 IU vitamin D3 and 1000 mg calcium daily or no treatment.
Outcomes	Fractures.
Notes	Published abstract. Email from Heikki Kroger 12/11/2007 to say publication being drafted.

Pfeifer 2004

Methods	One-year randomised controlled trial.
Participants	242 men and women aged over 70 years, in Germany.
Interventions	800 IU vitamin D3 and 1000 mg calcium or 1000 mg daily.
Outcomes	Falls and muscle power.
Notes	Published abstracts only. Possiblility of fractures reported in main report? No reply from email to author 11/2007.

Sato 2005

Methods	Two-year randomised controlled trial.
Participants	96 men and women with post-stroke hemiplegia, in Japan.
Interventions	1000 IU vitamin D2 daily or placebo.
Outcomes	Hip fractures/1000 patient years, deaths.
Notes	Further details required from authors.

Sosa 2000

Methods	Probably one-year randomised controlled trial.
Participants	70 women with previous hip fracture, in Spain.
Interventions	10,640 IU 25hydroxyvitamin D3/week and 1000 mg calcium/day or 1000 mg calcium/day.

Sosa 2000 (*Continued*)

Outcomes	Fractures.
Notes	Unclear if number of people with fractures or number of fractures reported. No reply to letter sent 10/02/2005.

Characteristics of ongoing studies *[ordered by study ID]*

Vital D

Trial name or title	Vital D: Primary care prevention of falls and fractures in the elderly by annual vitamin D supplementation
Methods	Randomised trial
Participants	Women aged 70+ years on entry. Need to score at least 5 on algorithm (higher risk of hip fracture or low vitamin D status). Exclusions: hypercalcaemia, vit D supplement > 400 IU/day, HRT and SERM, calcitriol, renal disease (creatinine > 150 umol/L), sarcoidosis, TB or lymphoma.
Interventions	Annual dose of 500,000 IU cholecalciferol or placebo.
Outcomes	Fractures (all sites, radiologically confirmed), fall rate (monthly ascertainment), total healthcare utilisation and mental health (depression).
Starting date	2003 (due to finish 2008)
Contact information	Dr Kerrie Sanders Clinical Research Unit Department Clinical and Biomedical Sciences; Barwon Health The University of Melbourne Geelong Hospital PO Box 281 Geelong 3220 Victoria, Australia. Email: KERRIE@BarwonHealth.org.au
Notes	

DATA AND ANALYSES

Comparison 1. Vitamin D [D2, D3 or 25(OH)D] versus control or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persons sustaining new hip fracture	9	24749	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.99, 1.33]
1.1 Not selected on the basis of previous osteoporotic fracture	6	21929	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.99, 1.35]
1.2 Selected on the basis of previous osteoporotic fracture	3	2820	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.72, 1.62]
2 Persons sustaining new non-vertebral fracture	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Not selected on the basis of previous osteoporotic fracture	1	3440	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.80, 1.15]
3 Persons sustaining new vertebral fracture or deformity	5	9138	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.42, 1.92]
3.1 Not selected on the basis of previous osteoporotic fracture	3	6393	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.36, 1.66]
3.2 Selected on the basis of previous osteoporotic fracture	2	2745	Risk Ratio (M-H, Random, 95% CI)	3.97 [0.44, 35.45]
4 Persons sustaining any new fracture	10	25016	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.09]
4.1 Not selected on the basis of previous osteoporotic fracture	7	22196	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.11]
4.2 Selected on the basis of previous osteoporotic fracture	3	2820	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.83, 1.21]

Comparison 2. Vitamin D [D2, D3 or 25(OH)D] and calcium versus calcium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persons sustaining new hip fracture	4	6988	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.61, 1.12]
1.1 Not selected on the basis of previous osteoporotic fracture	2	4307	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.44, 1.14]
1.2 Selected on the basis of previous osteoporotic fracture	2	2681	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.62, 1.36]

2 Persons sustaining new non-vertebral fracture	4	3061	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.79, 1.16]
2.1 Not selected on the basis of previous osteoporotic fracture	2	380	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.35, 1.27]
2.2 Selected on the basis of previous osteoporotic fracture	2	2681	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.81, 1.21]
3 Persons sustaining new vertebral fracture	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Selected on the basis of previous osteoporotic fracture	2	2681	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.77]
4 Persons sustaining any new fracture	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Not selected on the basis of previous osteoporotic fracture	2	927	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.48, 1.21]

Comparison 3. Vitamin D [D2, D3 or 25(OH)D] versus calcium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persons sustaining new hip fracture	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Selected on the basis of previous osteoporotic fracture	2	2718	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.61, 1.32]
2 Persons sustaining new non-vertebral fracture	3	2976	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.90, 1.31]
2.1 Not selected on the basis of previous osteoporotic fracture	1	258	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.57, 2.57]
2.2 Selected on the basis of previous osteoporotic fracture	2	2718	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.89, 1.31]
3 Persons sustaining new vertebral fracture or deformity	3	2976	Risk Ratio (M-H, Fixed, 95% CI)	2.21 [1.08, 4.53]
3.1 Not selected on the basis of previous osteoporotic fracture	1	258	Risk Ratio (M-H, Fixed, 95% CI)	2.59 [1.13, 5.95]
3.2 Selected on the basis of previous osteoporotic fracture	2	2718	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.29, 5.80]

Comparison 4. Vitamin D [D2, D3 or 25(OH)D] and calcium versus control or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persons sustaining new hip fracture	8	46658	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.73, 0.96]
1.1 Not selected on the basis of previous osteoporotic fracture	4	40524	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.71, 0.93]
1.2 Selected on the basis of previous osteoporotic fracture	4	6134	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.71, 1.47]
2 Persons sustaining new hip fracture: subgroup analysis by residential status (institution vs community)	8	46658	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.73, 0.96]
2.1 Resident in institution (nursing home, residential care etc)	2	3853	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.62, 0.92]
2.2 Community dwelling	6	42805	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.08]
3 Persons sustaining new non-vertebral fracture	9	46781	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.90, 1.00]
3.1 Not selected on the basis of previous osteoporotic fracture	5	40647	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.90, 1.01]
3.2 Selected on the basis of previous osteoporotic fracture	4	6134	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.10]
4 Persons sustaining new non-vertebral fracture: subgrouped by residential status (institution vs community)	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Resident in institution (nursing home, residential care etc)	2	3853	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.74, 0.98]
4.2 Community dwelling	7	42928	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.91, 1.02]
5 Persons sustaining new vertebral fracture	3	38990	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.75, 1.11]
5.1 Not selected on the basis of previous osteoporotic fracture	1	36282	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.75, 1.12]
5.2 Selected on the basis of previous osteoporotic fracture	2	2708	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.34]

Comparison 5. Alfacalcidol [1-alpha(OH)D3] versus control or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persons sustaining new hip fracture	4	371	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.05, 0.67]
1.1 Not selected on the basis of previous osteoporotic fracture	3	239	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.04, 0.69]
1.2 Selected on the basis of a previous osteoporotic fracture	1	132	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.04]
2 Persons sustaining new non-vertebral fracture	5	744	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.15, 1.00]
2.1 Not selected on the basis of previous osteoporotic fracture	2	466	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.15, 1.15]
2.2 Selected on the basis of previous osteoporotic fracture	3	278	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.12]
3 Persons sustaining new vertebral fracture	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Selected on the basis of previous osteoporotic fracture	1	132	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.33, 1.27]

Comparison 6. Alfacalcidol [1-alpha(OH)D3] and calcium versus calcium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persons sustaining new hip fracture	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Selected on the basis of previous osteoporotic fracture	1	113	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.00]
2 Persons sustaining new vertebral deformity	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Selected on the basis of previous osteoporotic fracture	3	259	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.20, 1.23]

Comparison 7. Alfacalcidol [1-alpha(OH)D3] versus calcium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persons sustaining new vertebral deformity	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Selected on the basis of previous osteoporotic fracture	1	23	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.52, 1.74]

Comparison 8. Alfacalcidol [1-alpha(OH)D3] versus vitamin D and calcium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persons sustaining new vertebral fracture or deformity	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Selected on the basis of previous osteoporotic fracture	1	148	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.29, 2.30]

Comparison 9. Calcitriol [1,25(OH)2D3] versus control or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persons sustaining new hip fracture	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Not selected on the basis of previous osteoporotic fracture	1	246	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.10]
2 Persons sustaining new non-vertebral fracture	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Not selected on the basis of previous osteoporotic fracture	1	246	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.18, 1.18]
3 Persons sustaining new vertebral deformity	3	327	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.40, 1.41]
3.1 Not selected on the basis of previous osteoporotic fracture	1	246	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.45, 35.28]
3.2 Selected on the basis of previous osteoporotic fracture	2	81	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.28, 1.10]

Comparison 10. Calcitriol [1,25(OH)2D3] and calcium versus calcium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persons developing new vertebral deformity	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Selected on the basis of previous osteoporotic fracture	1	86	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.58, 3.85]

Comparison 11. Calcitriol [1,25(OH)2D3] and vitamin D and calcium versus vitamin D and calcium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persons sustaining new vertebral deformity	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Selected on the basis of previous osteoporotic fracture	2	84	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.41, 1.52]

Comparison 12. Calcitriol [1,25(OH)2D3] versus calcium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persons sustaining new non-vertebral fracture	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Selected on the basis of previous osteoporotic fracture	2	663	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.09, 15.77]
2 Persons sustaining new vertebral deformity	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Selected on the basis of previous osteoporotic fracture	2	556	Risk Ratio (M-H, Random, 95% CI)	1.69 [0.25, 11.28]
3 Persons sustaining new vertebral deformity in Tilyard study	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Year 1	1	515	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.40, 1.58]
3.2 Year 2	1	476	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.26, 0.87]
3.3 Year 3	1	432	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.15, 0.52]

Comparison 13. Calcitriol [1,25(OH)2D3] versus vitamin D (with or without calcium in each group)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persons sustaining new non-vertebral fracture	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Selected on the basis of previous osteoporotic fracture	1	86	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.40, 3.37]
2 Persons sustaining new vertebral deformity	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Selected on the basis of previous osteoporotic fracture	2	96	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.55, 3.47]

Comparison 14. Vitamin D [D2, D3 or 25(OH)D] or any analogue with/without calcium: adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persons with hypercalcaemia	18	11346	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [1.59, 3.47]
1.1 Vitamin D [D2, D3 or 25(OH)D]	2	3034	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.15, 7.12]
1.2 Vitamin D [D2, D3 or 25(OH)D] and calcium	6	6583	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.81, 4.13]
1.3 Alfacalcidol [1-alpha(OH)D3]	6	741	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.85, 2.72]
1.4 Calcitriol [1,25(OH)2D3]	4	988	Risk Ratio (M-H, Fixed, 95% CI)	4.41 [2.14, 9.09]
2 Persons with gastrointestinal effects	11	47042	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [1.00, 1.08]
2.1 Vitamin D [D2, D3 or 25(OH)D] and calcium	7	45985	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [1.00, 1.08]
2.2 Alfacalcidol [1-alpha(OH)D3]	1	148	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.45, 2.44]
2.3 Calcitriol [1,25(OH)2D3]	3	909	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.66, 1.58]
3 Persons with renal disease (calculi or insufficiency)	11	46537	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.02, 1.33]
3.1 Vitamin D [D2, D3, 25(OH)D]	1	393	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.03, 16.01]
3.2 Vitamin D [D2, D3 or 25(OH)D] and calcium	4	44978	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.02, 1.33]
3.3 Alfacalcidol [1-alpha(OH)D3]	2	214	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.4 Calcitriol [1,25(OH)2D3]	4	952	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.34, 4.56]
4 Deaths	23	64423	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.93, 1.01]
4.1 Vitamin D [D2, D3, 25(OH)D]	3	8767	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.06]
4.2 Vitamin D [D2, D3 or 25(OH)D] and calcium	14	54203	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.89, 0.99]

4.3 Alfacalcidol [1-alpha(OH)D3]	3	535	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.20, 4.91]
4.4 Calcitriol [1,25(OH)2D3]	3	918	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.45, 4.01]

Comparison 15. Vitamin D [D2, D3 or 25(OH)D] and calcium versus control or placebo: subgroup analysis by residential status

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths	14	54203	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.89, 0.99]
1.1 Resident in institution (nursing home, residential care etc)	6	5919	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.86, 1.05]
1.2 Community dwelling	8	48284	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.88, 1.00]

FEEDBACK

Comment sent 19 August 1999

Summary

I note that the odds ratio is given as 0.68 at three years follow up for the outcome "Persons with new hip fracture in 3 years" for Chapuy 1992. However this differs slightly from the odds ratio presented in the original BMJ publication. Why do these two results differ and why don't the reviewers present odds ratio based on intention-to-treat analysis as presented in the analysis in this paper?

Reply

Thank you for pointing out this discrepancy. This occurred because, by mistake, we used the data for the total number of hip fractures sustained rather than those for the number of people sustaining one or more hip fractures. The corrected intention-to-treat analysis, presented in the review, yields the same odds ratio as in the BMJ article.

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WHAT'S NEW

Last assessed as up-to-date: 29 February 2008.

13 February 2009	New citation required but conclusions have not changed	An editorial oversight resulted in the omission of a new citation for the very substantial update of this review, published in Issue 1, 2009. Although there were no changes to the conclusions, the evidence base for this review was substantially augmented by the addition of eight new trials, contributing data from 44,827 participants.

HISTORY

Protocol first published: Issue 2, 1995

Review first published: Issue 3, 1996

31 October 2008	New search has been performed	In this update (Issue 1, 2009) we updated the search to October 2007. Eight new trials have been included with 44,827 participants. The conclusions of the review are unchanged for fracture prevention.
30 October 2008	Amended	Converted to new review format.
26 May 2005	New search has been performed	This review was substantively updated with 17 new studies in Issue 3, 2005. Eleven studies were awaiting assessment and three ongoing trials were identified. The conclusions were revised.
30 November 2000	New search has been performed	This review was substantively updated in Issue 1, 2001. Seven new studies were included and six studies awaited further evaluation. Five ongoing trials were identified. Small corrections were made to the results for hip fracture at three years for Chapuy 1992 in response to a reader's comment. The search strategy was updated. The methodological appraisal tool was revised In accordance with review group policy and the included studies re-scored. Data were analysed and presented as relative risk rather than Peto odds ratio. The reviewers' conclusions remained substantially unchanged.

CONTRIBUTIONS OF AUTHORS

In this update, all authors contributed to methodological appraisal and data extraction. A Avenell, WJ Gillespie and LD Gillespie drafted the update, and DL O'Connell provided statistical support, commented on the draft review and suggested changes. A Avenell is the guarantor of the review.

DECLARATIONS OF INTEREST

Prof Gillespie and Dr Avenell participated in the RECORD 2005 trial. Dr Avenell was the principal investigator for the Avenell 2004 trial. Neither carried out data extraction or quality assessment on trials they were involved with.

SOURCES OF SUPPORT

Internal sources

- Health Services Research Unit, University of Aberdeen, UK.

Computing, administration and library services (AA)

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INDEX TERMS

Medical Subject Headings (MeSH)

Bone Density Conservation Agents [*therapeutic use]; Calcitriol [therapeutic use]; Dietary Supplements; Fractures, Bone [etiology; *prevention & control]; Frail Elderly; Hydroxycholecalciferols [therapeutic use]; Osteoporosis [complications; *drug therapy]; Osteoporosis, Postmenopausal [prevention & control]; Randomized Controlled Trials as Topic; Vitamin D [analogs & derivatives; *therapeutic use]; Vitamins [*therapeutic use]

MeSH check words

Aged; Female; Humans; Male